

EFFECT OF SUBSTITUENTS IN AROMATIC HYDROGEN EXCHANGE

(An Examination of the Additivity Principle)

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ABSTRACT

The rates of detritiation in trifluoroacetic acid have been measured for all the ring-hydrogen sites of the polymethylbenzenes. Results for toluene and the xylenes are in agreement with those reported in the literature, but the rate for benzene is slower than that obtained by earlier workers.

The results show a general trend towards increasing departures from the Additivity Principle with increasing reactivity. The predictions of the Principle are consistently too high but deviations are found to be inexplicable in terms of substituent-reaction site steric interactions. Several modifications of the Principle are investigated.

The N.M.R. spectra of the polymethylbenzenes have been examined in carbon tetrachloride and in n-hexane. Solvent shifts previously attributed to steric hindrance have been shown to correlate much better with the chemical shift. For both ring and methyl protons satisfactory prediction of chemical shifts by an additive relationship is possible only if large second order interactions between adjacent methyl substituents are admitted. It appears possible that such interactions may affect the behaviour of substituents in the detritiation reaction.

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## INTRODUCTION

### (A) General

#### (i) Scope of the Work

The work to be described in this thesis provides a direct test of the Additivity Principle for multiple substitution. Earlier work<sup>1,2</sup> had shown that product distributions for nitration in acetic anhydride could not be reconciled with additivity predictions and led to the choice of a exchange reaction, proto-detritiation, in the hope that steric effects would be small. The methyl group was selected as the substituent to be studied because relatively simple synthetic routes were available to the tritium labelled polymethylbenzenes. Previous tests of the Additivity Principle had also utilised the methyl group.<sup>3</sup>

This kinetic study of the methyl group was supplemented by a proton magnetic resonance study of the polymethylbenzenes in which chemical shifts and solvent shifts were measured for both ring and methyl hydrogen atoms.

The description and discussion of the present work is preceded by a brief guide to the many reviews of relevant previous work.

#### (ii) Use of Statistics

Extensive use has been made of computer facilities for

statistical analyses. For convenience in handling multi-parameter regression analyses, many graphs are shown as plots of observed values (vertical axis) versus calculated values (horizontal axis), so that the least squares line has unit slope. The "slope" and "intercept" of conventional plots are thus used to define the position of the points on these graphs, and are obtained as the regression parameters, not directly from the graphs.

Errors are statistically estimated and are quoted in standard form. No attempt is made to deduce absolute error limits for the measurements, although where a standard deviation ( $\sigma$ ) is well established errors larger than  $2\sigma$  are unlikely.

(B) Aromatic Electrophilic Substitution

(i) Other Substitution Reactions

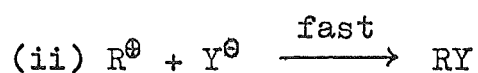
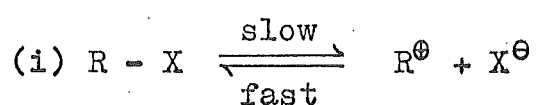
The conjugated cyclic  $\pi$ -electron systems characteristic of aromatic molecules are not susceptible to addition reactions of the type readily undergone by other unsaturated systems. The preferred reaction is usually substitution, a displacement of the atom, or group of atoms, attached directly to one of the carbon atoms of the aromatic ring. When the attacking species is electron deficient it is termed an electrophile, and the leaving or displaced group usually bears a formal positive charge, while part or the whole of the electrophile remains attached to the ring. As the leaving group is also electrophilic the reverse reaction is possible, and the system "relaxes" towards an equilibrium distribution of products.

Aliphatic substitution reactions are described by two model mechanisms.<sup>4</sup> " $S_N1$ " reactions show first order kinetics. They are interpreted by assuming that the rate-determining step is an initial unimolecular heterolytic bond-breaking process. The resulting organic ion which has lost a substituent in this manner then links up with an oppositely charged ion from the reagent solution in a fast recombination. " $S_N2$ " reactions show second order kinetics, and are described by a single bimolecular step

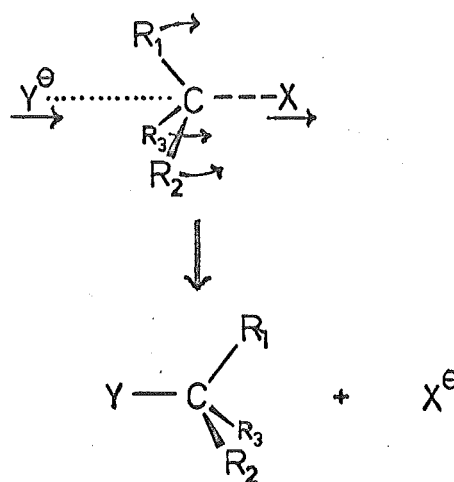
in which the attacking species approaches along the axis of the bond to be broken but from the opposite side of the carbon atom at which substitution occurs. Synchronously with this approach, the leaving group is released and the three other bonds of the  $sp^3$  hybridised carbon atom move away from the attacking species as shown in Figure 1. The geometry of the product is then "inverted" with respect to the reagent.

FIGURE 1

Reaction Models for Aliphatic Substitutions



Unimolecular Process



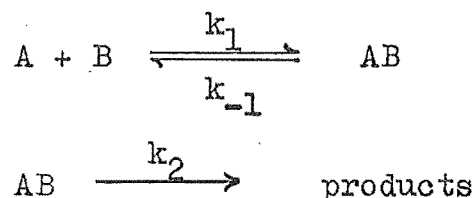
Bimolecular Process



(ii) Kinetic Form of Electrophilic Aromatic Substitution

Electrophilic aromatic substitution reactions usually exhibit second order or more complex kinetics. However, work by Melander<sup>5</sup> showed that the effects of isotopic substitutions made in the leaving group were much smaller than predicted by a synchronous  $S_N2$  process. Later work has shown that a wide range of isotope effects may be observed in aromatic substitution, but Melander's conclusions have not been challenged.<sup>6,7</sup> Melander deduced that the process could not be considered as a single step, but must involve an activated complex capable of reverting to reactants as well as decomposing to products.

Consider the following reaction sequence:-



Since  $-d[AB]/dt = (k_{-1} + k_2) \cdot [AB] - k_1 \cdot [A][B]$   
the assumption that  $[AB]$  is small and constant (the "steady-state" assumption) leads to the expression:-

$$\begin{aligned} [AB] &= [k_1 / (k_{-1} + k_2)] \cdot [A][B] \\ \text{Then } -d[A]/dt &= k_1 \cdot [A][B] - k_{-1} \cdot [AB] \\ &= [k_1 k_2 / (k_{-1} + k_2)] \cdot [A][B] \\ &= k_{\text{obs}} \cdot [A][B] \end{aligned}$$

This more complex process still obeys second order kinetics, but the observed rate-constant is a function of the three rate-constants describing the components of the overall reaction. If  $k_2$  is large compared with  $k_{-1}$  then  $k_{\text{obs}} = k_1/k_{-1}$  and the first step is rate-determining. Since little bond-breaking occurs in the formation of the activated complex, AB, isotope effects will be small when  $k_2$  is large.<sup>6</sup>

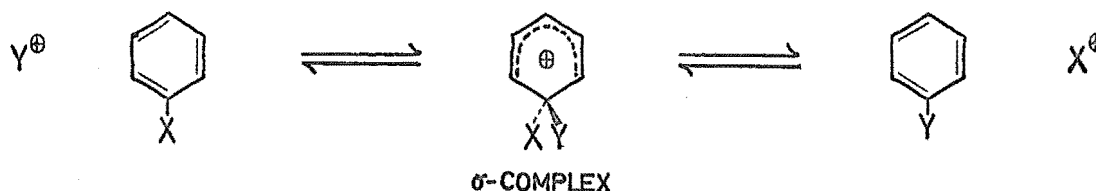
(iii) The  $\sigma$ -complex

The generally accepted model of the activated complex is the Wheland intermediate ( $\sigma$ -complex.)<sup>8</sup> Assuming the electrophile attacks the  $\pi$  electrons of the conjugated system at a reactive carbon atom, whose hybridisation is thereby transformed from  $sp^2$  to  $sp^3$ , the Wheland intermediate contains five conjugated atoms, and the  $\pi$  orbitals of this limited system are occupied by only four electrons. The intermediate is a cation which has lost a major portion of the resonance energy of the neutral aromatic molecule, but the charge is delocalised mainly over the ortho and para positions relative to the site of attack.<sup>9</sup>

Several  $\sigma$ -complexes have been isolated as salts where special features provide exceptional stability.<sup>10</sup> Strongly acidic media have been used to produce sufficiently concentrated solutions of protonated aromatics for N.M.R.

studies to be made.<sup>11,12</sup> All these confirm the structure shown in Figure 2.

FIGURE 2



In normal cases the  $\sigma$ -complex represents a highly activated configuration present in very small concentrations, and as such it is believed to approximate closely to the "transition state" of the reaction in which it is formed. (By Hammond's postulate<sup>13</sup> molecular structures occurring sequentially during a reaction are of similar geometry if their energy contents are similar. As the  $\sigma$ -complex is of much higher energy than the reactants, it follows that the transition state must be more like the  $\sigma$ -complex than the reactants. The same argument may be applied to the second step of the substitution.)

(iv) The  $\pi$ -complex

A second type of association between aromatic and electrophile has been suggested to cover several diverse phenomena.<sup>14</sup> In weaker acids than those used to observe  $\sigma$ -complexes, and in cases where steric hindrance makes

$\sigma$ -complexes unfavoured, it has been suggested that a more loosely-bound  $\pi$ -complex is formed by donation of  $\pi$ -electrons from the aromatic to the electrophile. This bond is not considered to be specific to any particular carbon atoms of the aromatic ring, and is usually represented as shown below.

FIGURE 3



The relative importance of  $\pi$ -complexes in substitution reaction mechanisms has been the subject of some controversy.

Work by Olah on nitration by nitronium ion salts (e.g.  $\text{NO}_2^+\text{BF}_4^-$ ,  $\text{NO}_2^+\text{ClO}_4^-$ ) showed that substituent effects were quite large as shown by competition between the various sites of a single molecule, but that there was surprisingly little selectivity between competing molecules.<sup>15</sup> This was interpreted as demonstrating that some kind of  $\pi$ -complex formation was rate-determining with subsequent selection of the more reactive sites of the molecule for  $\sigma$ -complex formation leading to the observed products. It has been pointed out that the extremely fast nature of the reaction may cause localised depletion of the more reactive aromatic substrates in spite of strenuous efforts to achieve mixing during addition of the nitrating agent.<sup>16</sup> Until this possibility is eliminated it is unnecessary to postulate

rate-determining  $\pi$ -complex formation to explain these results. In less reactive systems intermolecular reactivity is usually well described by direct competition between the possible  $\sigma$ -complexes, and although  $\pi$ -complexes may occur they do not appear to be kinetically significant.

(v) Correlation of Substituent Effects

Although the theory of absolute reaction rates as developed by Eyring and his co-workers<sup>17</sup> cannot be used to calculate reaction rates a priori until much more detailed knowledge is available concerning the transition states of reactions, considerable progress has been made towards quantitative assessments of the modifications of reactivity caused by substituents. Following the success of the Hammett treatment of side-chain reactions of aromatic molecules extensions to direct substitution reactions have been investigated. For the simple Hammett-like relation

$$\log k/k_H = \rho\sigma$$

successful correlations require large  $\rho$  values to account for the greatly increased sensitivity to substituents compared with side-chain reactions.<sup>3</sup> Substituents

intrinsically capable of resonance donation show greatly enhanced activation towards electrophilic substitution

when placed ortho or para to the reaction site.<sup>18</sup> When placed in the ortho position substituents of varying steric requirements cause deviations from the linear relationship

according to the steric requirements of the reaction.<sup>19</sup>  
 (Both steric hindrance and steric acceleration are possible depending on the relative sizes of the attacking and leaving groups.) Resonance contributions to the transition state can also be hindered if a substituent is forced into an unfavourable orientation by steric factors.

The relation between the behaviour of a given substituent in the various positions relative to the reaction site has also been investigated. In particular, the substituent effects have been analysed into two parts, inductive and resonance.<sup>20</sup> Inductive effects are said to operate where no unsaturated linkages exist between substituent and reaction site. The relative importances of transmission of this effect through the bonding electrons and by direct electrical field effects have not been clearly established.<sup>21</sup> The resonance effects show their importance in electrophilic substitution most clearly for several substituents, (e.g. the methoxy group) which deactivate if placed in the meta position, but activate when placed in the ortho and para positions. In fact it has been shown that except for these substituents several good correlations exist between the various types of  $\sigma$  values proposed to account for different reaction site-substituent pathways.<sup>22</sup>

Recent work has successfully extended these studies to the naphthalene series using the four parameter relation due to Taft.<sup>23</sup>

$$\log k/k_H = \rho_I \cdot \sigma_I + \rho_R \cdot \sigma_R$$

(C) The Additivity Principle

A simple solution to the problem of multiple substitution was proposed by Condon.<sup>24</sup> He suggested that a given substituent in a given position made a characteristic contribution to the free energy of activation, and that if more than one substituent was present the resultant contribution was simply the algebraic sum of those observed for mono-substitution; thus

$$\delta\Delta G = \sum_S \delta_S \Delta G^\ddagger$$

is the modification to the free energy of activation caused by a set of substituents (S) for which  $\delta_S \Delta G^\ddagger$  is the modification observed in the mono-substituted compound.

Also  $2.303RT \log k/k_H = -\delta\Delta G^\ddagger$

where H denotes the unsubstituted compound, and this equation is derived from the absolute rate theory.<sup>17</sup>

$$\therefore k/k_H = \exp\left(-\sum_S \delta_S \Delta G^\ddagger / 2.303RT\right)$$

$$= \prod_S \exp(-\delta_S \Delta G^\ddagger / 2.303RT)$$

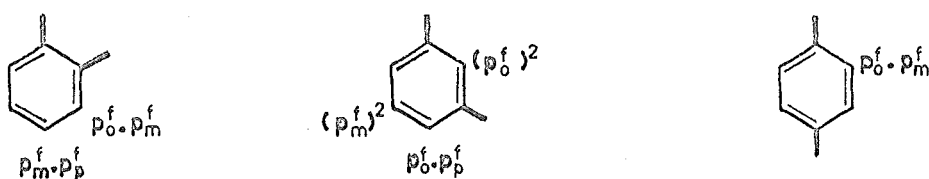
$$= \prod_S k_S/k_H$$

where  $k_S/k_H$  is the ratio of reactivities of a given reaction at a particular site with and without the substituent S.

For example, the ratios of the reactivity at the ortho, meta,

and para positions of toluene relative to one position of benzene, define three constants that can be used to predict reactivities for the polymethylbenzenes. Using the nomenclature  $p_S^f = k_S/k_H$  where  $p^f$  is a "partial rate factor", and labelling the three positions of the methyl group o, m, and p, calculated reactivities relative to benzene for the different positions of the xylenes are shown below.

FIGURE 4



Partial Rate Factors for the Xylenes

The additivity principle has been tested by measurements of overall molecular reactivities of the polymethylbenzenes for bromination, chlorination, mercuration, benzylation, and deuteration.<sup>25</sup> (See pages 89-90.) Agreement is satisfactory except where steric requirements are large. Decreased reactivities for the higher polymethylbenzenes are usually observed, however. Some reactions involving displacement of groups other than hydrogen have facilitated examination of the reactivities at specific positions. Unfortunately,



deviations clearly due to steric effects are observed.<sup>19</sup>

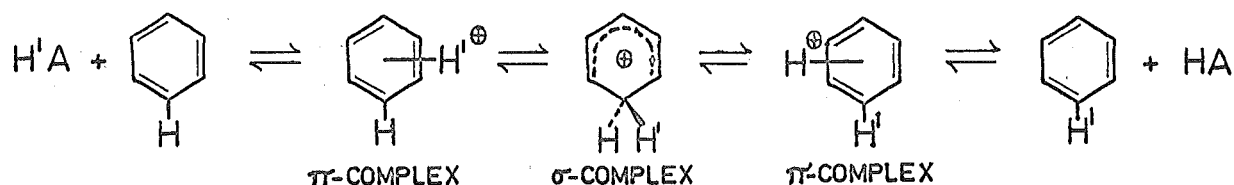
The present work arose from problems encountered in explaining the results of nitration of the trimethylbenzenes and xylenes.<sup>1,2,26</sup> Although complicated by acetylation as a side reaction no reconciliation with the additivity principle has so far been possible. The advantages of detritiation as a guide to electronic effects are discussed in the next section.

The Additivity Principle has received extensive attention in the reviews by Stock and Brown,<sup>3</sup> Baciocchi, and Illuminati,<sup>25</sup> and Norman and Taylor.<sup>19</sup>

(D) Hydrogen Exchange(i) Hydrogen Exchange as an Electrophilic SubstitutionReaction

The proton is the smallest chemical electrophile and offers the possibility of small steric requirements if it can be obtained free from a strongly attached solvent "shell". As hydrogen atoms form bonds to a very wide range of other elements, an almost infinite range of electrophilic reactivities can be obtained. These can only be observed in electrophilic substitution, however, if the proton is still partially attached to the conjugate base (of the reagent acid) in the rate-determining transition state.

For the aromatic exchange reaction the possible reaction sequence shown in Figure 5 has been suggested.<sup>27</sup>

FIGURE 5A-1 Model for Hydrogen Exchange

It can be seen that if  $k_2$  represents the rate-determining step then this will be largely independent of A.

The rate of hydrogen exchange will follow the simplified relation

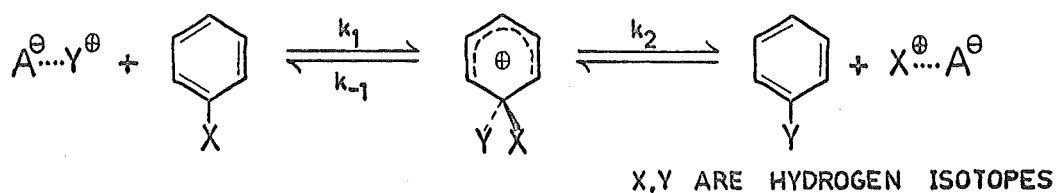
$$-d \ln [S] / dt = k_H [H^+]$$

compared with that for the  $A_{SE}^2$  mechanism (Figure 6) for which the relation

$$-d \ln [S] / dt = k_H [H^+] + \sum_A k_{HA} [HA]$$

is predicted. A study of reactivities in buffered solutions can in principle distinguish between the two forms. In practice solvent dependence studies have given conflicting evidence, and the  $A_{SE}^2$  mechanism now appears to have more general application. Since the solvent markedly affects the behaviour of substituents, as evidenced by the reversal of the Baker-Nathan order ( $t\text{-Bu} < \text{Me}$ ) on changing from sulphuric acid to trifluoroacetic acid media,<sup>28</sup> it is not surprising that discrepancies have been found for treatments which consider only the interaction of A with the proton transferred.

FIGURE 6



$A_{SE}^2$  Model for Hydrogen Exchange

The steady-state approximation has previously been applied to the  $A_{SE}2$  mechanism (page 5). With the notation of Figure 6;

$$k_{obs} = k_1 k_2 / (k_{-1} + k_2)$$

From the similarity of the several isotopes of hydrogen we expect that  $k_{-1}$  and  $k_2$  will be of the same order of magnitude. (The second step would also be reversible if the concentration of tritium atoms was comparable to the concentration of protons in the acid medium.)

It can be shown that differentiation of the steady-state equation leads to the expression

$$d(\ln k_{obs}) = d(\ln k_1) + [d(\ln k_2) - d(\ln k_{-1})] / (1 + k_2/k_{-1})$$

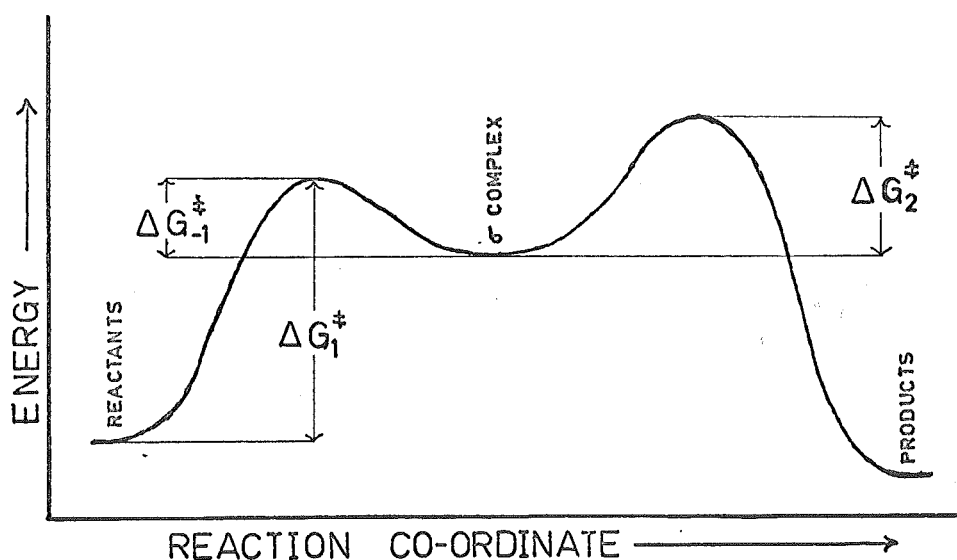
Since  $d(\ln k) = -d(\Delta G^\ddagger / RT)$  from the absolute rate equation

$$d(\Delta G_{obs}^\ddagger) = d(\Delta G_1^\ddagger) + [d(\Delta G_2^\ddagger) - d(\Delta G_{-1}^\ddagger)] / (1 + k_2/k_{-1}).$$

These energies are illustrated in Figure 7. (See page 17.)

Perturbations of the activation energies such as those produced by substitution will probably cause similar changes in the quantities  $\Delta G_{-1}^\ddagger$  and  $\Delta G_2^\ddagger$ . The above equation then shows that the change in the free energy calculated from the overall rate-constant is a good measure of the change in  $\Delta G_1^\ddagger$ , and hence the stability of the first transition state. Good agreement with Hammett correlations can then be expected in spite of the apparent complexity of the observed rate-constant.

FIGURE 7

Reaction Profile for  $A_{SE}^2$ 

(ii) Experimental Techniques for Measurement of Hydrogen Exchange

Techniques for the measurement of hydrogen exchange have been well established. Isotopic substitution enables the reaction to be treated as an ordinary transformation of reagents into products, chemically distinguishable by N.M.R. and mass spectroscopy for deuterium, and by liquid scintillation counting in the case of tritium. Tritium has the advantage of requiring only tracer levels of substitution, and the method of analysis is more suited to large numbers of samples.<sup>29</sup>

As previously noted displacement reactions allow prior

selection of the reaction site to be observed. Hydrocarbons can be labelled by reaction of a Grignard reagent (derived from the appropriately substituted bromohydrocarbon) with either  $D_2O$  or tritiated water. The rate of exchange of this label when the hydrocarbon is reacted with protons from a suitable acid can then be measured. Pure trifluoroacetic acid (at  $70^\circ C$ ) has been found to be a good solvent and to afford high acidity without interfering side-reactions (e.g. sulphonation where sulphuric acid is used). Detritiation under these conditions has been shown to be sensitive to the methyl group as a substituent, to obey pseudo first order kinetics, to have apparently small steric requirements and, for the xylenes, to exhibit only small deviations from the Additivity Principle.<sup>30</sup> These investigations by Eaborn and his co-workers also indicated that it should be possible to measure the reactivities of a large number of the positions of the polymethylbenzenes under these conditions, enabling confident comparisons to be made.

In fact the deviations from Additivity found in the present work reduced the expected spread of rates so that only isodurene and pentamethylbenzene eventually had to be measured at lower temperatures.

(iii) Results of Previous Work

Results for hydrogen exchange under the conditions chosen for the present work (trifluoroacetic acid at 70°C) have been obtained for detritiation and for deuteration. These are compared with the results obtained in the present work in the Discussion. (Pages 74 and 103 respectively.) Detritiation results were not available for the trimethylbenzenes or the higher polymethylbenzenes. The deuteration results covered the whole range of polymethylbenzenes, but referred to overall reactivities rather than those of the individual ring positions, and they also involved approximate temperature extrapolations.<sup>31,32</sup>

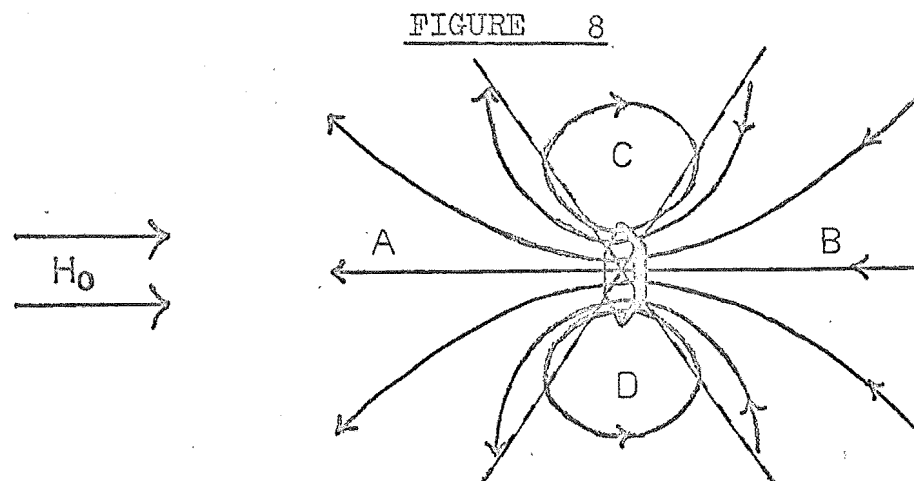
Results using a variety of other conditions have been surveyed by Norman and Taylor<sup>19</sup> and cover a very limited range of the polymethylbenzenes.

(E) N.M.R. Studies of the Protons of the Polymethylbenzenes

(i) Chemical Shifts

When a substance is placed in the applied magnetic field of a nuclear magnetic resonance spectrometer, the various chemically-distinguishable protons occurring in the substance experience different resultant magnetic fields because of the existence of small local fields. When a liquid is being observed, the molecules tumble and so experience almost random orientations with respect to the applied field. The time-averaged signals observed in the resonance measurement therefore are affected only by local fields which are dependent upon the direction of the applied field. Such fields are produced when molecular motion couples with the applied field to induce electronic motion.

The conjugated rings of aromatic molecules provide a low energy path for electronic motions, and behave like circular conductors when moved in an applied magnetic field.



Field Produced by Induced Ring Current in Benzene



As shown in Figure 8 the environment of the ring includes both shielding regions (A, B) and deshielding regions (C, D) so that relative positions determine the influence of a ring current on a particular proton.

In a similar fashion electron circulations in more restricted orbitals generate magnetic fields. Protons are thus invariably shielded by their bonding electrons. Effects due to more distant electrons are dependent on orbital anisotropies. For example, consider the situation in Figure 8 when  $H_0$  is perpendicular to the illustrated direction. If the ring could now sustain a current which produced a field opposing  $H_0$ , A, B would become deshielding regions and C, D would become shielding. Thus, the existence of a net effect at positions other than the centre of the ring is dependent on the difference between the magnetic susceptibilities in two perpendicular directions.

Because a proton is substantially shielded by its bonding electrons, its chemical shift is sensitive to changes in the electronegativity of the atom bonded to the proton. This is the basis of the relation of chemical shifts to changes in reactivities which has been established by Taft's set of  $\sigma_F$  values derived from fluorine chemical shifts for a wide variety of substituents.<sup>33</sup>

There have been many reviews of the theory of chemical shifts.<sup>34,35,36</sup>

### (ii) Solvent Effects

Considerable interest is being shown in solvent effects on chemical shifts in N.M.R. studies.<sup>37</sup> Williams and his co-workers have examined a limited range of the polymethylbenzenes in several solvents and concluded that steric effects are important. Extended studies have been made on benzene solvent shifts,<sup>37,38</sup> and results have been interpreted in terms of preferred specific orientations of the benzene molecules with respect to the solute molecules.

In order to detect any solvent induced anomalies in the present work measurements were made in both carbon tetrachloride and n-hexane.

### (iii) Previous Work

A number of studies have been made of the chemical shifts of the protons of the polymethylbenzenes. For example, Reddy,<sup>39</sup> Alexandrou,<sup>40</sup> and Lewis<sup>41</sup> have made measurements for some members of the series using carbon tetrachloride as a solvent.

It has been suggested by Williams and his co-workers<sup>42</sup> that  $\text{CCl}_4$  solvation effects are dependent on steric hindrance. None of these experiments covered the complete range of polymethylbenzenes, and the possibility of an additive relationship for the effects of substitution had not been properly examined. The present work investigates these aspects.

## EXPERIMENTAL

### (A) Preparation of Specifically-Labelled

#### Polymethylbenzenes

Isomerically pure samples of the halo-polymethylbenzenes were used to form Grignard reagents which were decomposed by tritiated water. This results in specific labelling at the site of the original halogen atom with an activity depending on that of the tritiated water and on the adverse isotope effect. ( $k_H/k_T = 3-4$ )<sup>43</sup>

#### (i) Gas-Liquid Chromatography

As the boiling points of the bromopolymethylbenzene isomers are within a few degrees of each other and only bromodurene and bromopentamethylbenzene are readily crystalline at room temperature, purification control relied heavily on chromatographic and spectral techniques. Thin-layer chromatography was not found helpful in distinguishing between these isomers so the versatility of gas chromatography was exploited.

The following columns were prepared by packing under pressure.

1. 5% PEGA (polyethyleneglycoladipate) on 60/80 mesh Chromosorb P in a 5ft x 1/8in O.D. copper column.

The same solid support and column shell specifications apply to all columns unless otherwise stated.

2. 5% PEGA in a 12ft x 1/8in O.D. copper column.
3. 5% QF-1 (fluoro-silicone)
4. 5% SE-52 (phenyl-silicone)
5. 5% XF-1150 (cyano-silicone)
6. 2.5% QF-1 on Aeropak 30 in a 20ft x 3/32in O.D. copper tube. This has half the inside diameter of the ordinary 1/8in tubing and is of the 'Micropak' (Varian-Aerograph) type. As a semi-micro column it could be used without a stream splitter but resolution improved greatly as sample size was decreased. Carrier flow was too slow to monitor but was maintained by a 20lb input pressure.
7. 2.5% QF-1 on Aeropak 30 in a 4ft x 3/8in O.D. aluminium column.
8. MEM (m-bis-m-phenoxybenzene) in a 200ft x 0.01in I.D. stainless steel column. This was a Golay column supplied by Perkin-Elmer.
9. QF-1 in a 200ft x 0.01in I.D. stainless steel column. This was made from an old Golay column by washing with dichloromethane and nitric acid and then blowing a 'plug' of QF-1 dissolved in dichloromethane and a little Tergitol (this blocks any active sites) through the column.<sup>44</sup> This column appeared to lose its liquid phase after about

20hrs use.

10. 5% SE-30 (silicone gum rubber) on 60/80 mesh Chromosorb W in a 5ft x 1/8in O.D. stainless steel column.

Most columns were used in a Varian Aerograph Model 1200 HI FI III with an alloy flame ionisation detector using nitrogen as the carrier gas controlled by a Differential Flow Controller. Injections were made on-column.

The Golay columns required a stream splitter and were used either in a Perkin-Elmer F-11 or a Micro-Tek Model 2500 II. An Aerograph Autoprep Model 700 was used for preparative work.

Peak areas were assumed to be linearly related to carbon content and were measured by a Kent Chromalog Integrator or estimated as the product of the width at half height x height.

Of all the liquid phases tried PEGA and QF-1 were by far the best at resolving the aromatic bromo isomers. QF-1 was the superior because its lower viscosity allowed it to be used below 100°C where PEGA no longer solvated well. The Golay columns were very easy to overload and suffered from long retention times but remained the last resort. The semi-micro (Micropak) column proved an excellent compromise and was used in most of the analyses.

TABLE 1

G.L.C. Analyses of Bromopolymethylbenzenes

<u>Compound</u>	<u>Column</u>	<u>Temperature</u>	<u>Retention</u>	<u>Resolution</u>
	(Page 24)	(°C)	<u>Time</u> (min)	
<u>Bromotoluenes</u>	8	100		
ortho-			70	
meta-			74)	1/3 height
para-			73)	
<u>Bromo-orthoxylenes</u>	3	65		
3-			10)	1/4 height
4-			12)	
<u>Bromometaxylenes</u>	6	70		
2-			17 )	1/4 height
4-			18.5)	
<u>Bromopseudocumenes</u>	8	140		
3-			55)	1/4 height
5-			56)	
6-			61	
<u>Bromohemimellitenes</u>	6	80		
4-			40.5)	1/8 height
5-			44.5)	
<u>Bromotetramethyl-</u>				
<u>benzenes</u>	6	125		
bromoprehnitene			10	
bromo-isodurene			8.5)	not
bromodurene			8.0)	resolved

SE-30 is the best for scanning for impurities of widely differing boiling points, and XF-1150 proved satisfactory for isomeric anilines and also for low boiling solvents.

(ii) Spectrometers

Infrared spectra were run on a Perkin Elmer 337 Grating Spectrometer and compared with spectra published in the D.M.S. card system or in other literature.

N.M.R. spectra were run on a Varian A60 instrument in carbon tetrachloride using T.M.S. as an internal reference.

Mass Spectra were run on an AEI MS902 spectrometer.

(iii) Distillations and Recrystallizations

Difficult separations were carried out in a 24in Nester-Faust annular teflon spinning band or an 18in Nester-Faust goldplated spinning band column. Other distillations were carried out with 3in-6in vigreux columns or with a 6in glass helices column. Simple distillations of small quantities were carried out in a short-path apparatus similar to that for sublimation. Solvent could be removed under reduced pressure by inserting a capillary tube in the line to the pump and so ensuring a steady boil off without an air bleed.

Low temperature fractional recrystallizations were

carried out in a refrigerated room to minimize icing. The mother liquor was removed with a syringe to avoid melting the crystals during filtration.

(iv) Preparation of the Bromopolymethylbenzenes

All compounds were considered pure if less than 0.5% impurities were detected. Infrared spectra were compared with the literature, usually with the D.M.S. card system.<sup>45</sup> G.L.C. analyses were performed on at least two columns for all compounds - column (10) to scan a wide range of boiling points and another column to show isomeric purity. (The column numbers refer to those on page 25.) G.L.C. Retention times of the aryl bromide isomers are shown in Table 1.

Bromobenzene (Hopkin and Williams G.P.R. grade) was examined on column (6) and no impurities could be detected. The infrared spectrum compared exactly with that in the literature.

p-Bromotoluene (Hopkin and Williams A grade) was examined on column (8) at 100°C. The commercial sample of p-bromotoluene showed no evidence of the other isomers. The infrared spectrum showed no trace of the peaks at  $683\text{cm}^{-1}$  and  $746\text{cm}^{-1}$  characteristic of the meta and ortho isomers respectively.<sup>46</sup>



o-Bromotoluene (Fluka "Pariss" grade) showed about 2.5% of meta or para isomer on column (8). No peak was observed at  $476\text{cm}^{-1}$  (p-bromotoluene) in the infrared spectrum indicating the meta isomer as the impurity. Recrystallization from pentane using dry-ice/acetone reduced the impurity to 1%. (m.p.s.  $-26^{\circ}\text{C}$ ,  $-40^{\circ}\text{C}$ ,  $+28.5^{\circ}\text{C}$  for o, m, p-bromotoluenes respectively)

m-Bromotoluene (L.Light) showed a trace of the ortho isomer (1%) on column (8). The infrared did not offer conclusive evidence about the possibility of either isomeric impurity. Recrystallization from pentane using dry-ice/acetone reduced the ortho isomer to 0.3%.

4-Bromo-o-xylene (Aldrich) was shown to contain about 15% of the 3-bromo isomer using column (3). This impurity (b.p.  $211.5$ ) was removed by distillation under reduced pressure using a Nester-Faust annular spinning-band column, and a fraction of 4-bromo-o-xylene (b.p.  $214.5^{\circ}\text{C}$ ) showing no detectable impurity was obtained.

2-Bromo-m-xylene (Aldrich) was purified by distillation using the annular spinning-band column and showed no impurities on column (6) or N.M.R.

Another isomerically pure sample was made from recrystallized 2,6-dimethylphenol (L.Light) using the

method of Schaefer and Higgins.<sup>47</sup> Triphenylphosphine was brominated in acetonitrile and the phenol added to form a complex which was decomposed at 200-300°C, the required bromo-xylene boiling off. (Yield 60%) The only impurity was some m-xylene.

4-Bromo-m-xylene (Fluka "purum" 99% G.C.) showed about 10% of the 2-bromo isomer on column (6), confirmed by N.M.R. As these isomers were very difficult to separate even on G.L.C. it was not thought practicable to separate them by distillation.

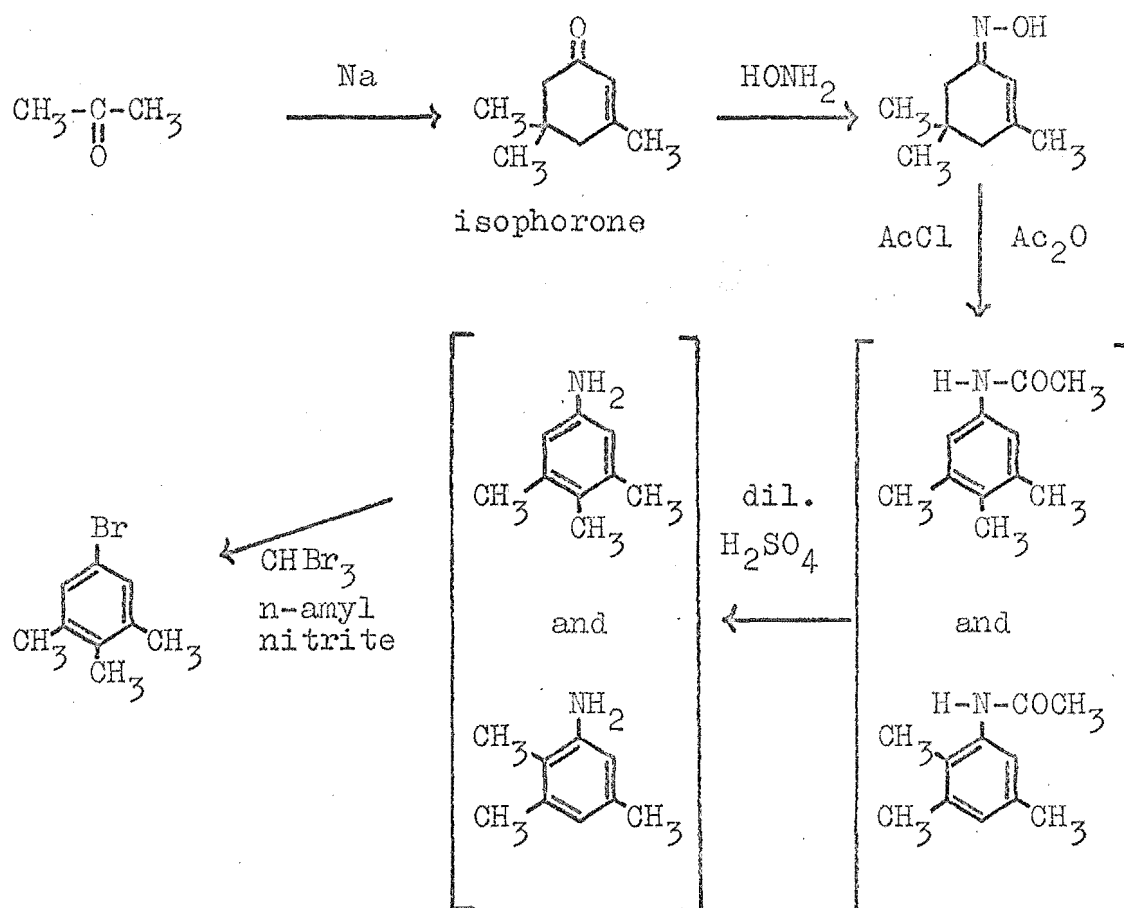
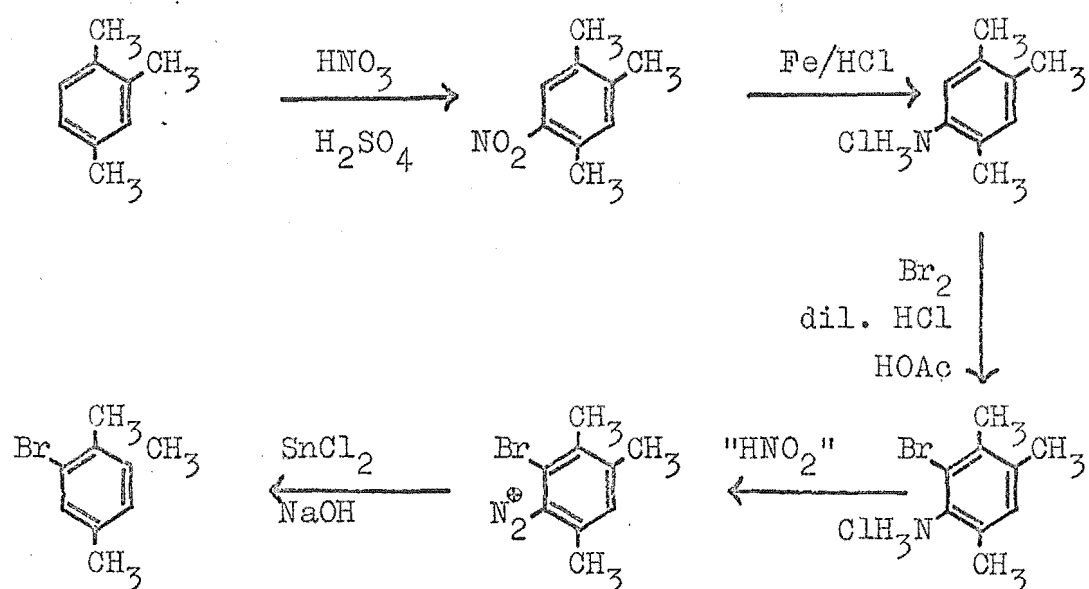
Isomerically pure 4-bromo-m-xylene was prepared from 2,4-dimethylphenol (B.D.H.) by the method of Schaefer and Higgins.<sup>47</sup> (Yield 30%)

5-Iodo-m-xylene was prepared from the corresponding xylidine. 3,5-Dimethylaniline (Aldrich) was distilled under reduced pressure and shown to contain one peak on column (5). Diazotisation of the amine dissolved in a mixture of aqueous hydrochloric acid and tetrahydrofuran, and reaction of the diazonium salt with potassium iodide overnight gave the 5-iodo-m-xylene and a considerable amount of phenolic impurity. After distillation the product appeared to be pure on column (3) and infrared.

2-Chloro-p-xylene (Fluka "purum" 99% G.C.) was analysed on column (8), infrared, and N.M.R. No impurities could be detected.

4-Bromohemimellitene was prepared by bromination of hemimellitene with bromine in chloroform.<sup>48</sup> Commercial hemimellitene (L.Light) was shown to be pure on column (12). The brominated product showed no detected isomeric impurity on columns (6) and (9), or by N.M.R.

5-Bromohemimellitene was prepared from 5-amino-hemimellitene which was made from isophorone by the method of Beringer and Ugelow.<sup>54</sup> Isophorone was prepared by reacting sodium wire (100g) with dry acetone (100g) cooled in an icebath. A vigorous reaction occurred and a brown layer formed on the surface. Methanol was added to destroy any unreacted sodium and then the mixture was poured onto ice. The acetone was removed by flash distillation through a short column and the organic material obtained by steam distillation and extraction into dichloromethane. The 278g of liquid obtained was distilled through a short vigreux column and two fractions collected. (b.p. 75-90°C at 4mm and 90-100°C at 4mm) The lower-boiling fraction was distilled through a Nester-Faust spinning-band column and the main fraction,

Preparation of 5-BromohemimellitenePreparation of 6-Bromopseudocumene

95g of clear liquid, b.p.  $60^{\circ}\text{C}$  at 2.5mm, was collected and shown to be better than 98% pure isophorone by column (5) and infrared. (Yield 10%)

Isophorone oxime was prepared in 85% yield by reaction of isophorone and hydroxylamine in pyridine and methanol. The oxime was reacted with acetyl chloride in acetic anhydride and pyridine to form a mixture of 3,4,5-trimethylacetanilide and 2,3,5-trimethylacetanilide by methyl migration and aromatization. Total yield 73g (80%).

The mixed acetanilides were refluxed with 20% sulphuric acid to yield the anilines. After distillation and recrystallisation from pentane/hexane mixtures 24.7g (45%) of 5-aminochemimellitene was obtained and appeared pure on column (5).

19g of 5-aminochemimellitene was reacted with 22.7g of freshly-prepared n-amyl nitrite in bromoform (80ml) at  $100^{\circ}\text{C}$  for 1hr. Elution of the crude material with pentane on silica gel gave 5-bromohemimellitene (8.5g, 33%) shown to be pure on columns (6) and (9), and by infrared.

3-Bromopseudocumene was prepared by the method of Lowe, Torto, and Weedon.<sup>49</sup> Pseudocumene (L.Light) was shown to be free of other hydrocarbon isomers by

G.L.C. analyses and was sulphonated with concentrated sulphuric acid, yielding pseudocumene-5-sulphonic acid. This was then brominated with bromine in the sulphuric acid solution and the water-soluble fraction separated from the tribromopseudocumene. The 3-bromopseudocumene-5-sulphonic acid obtained was hydrolysed with steam in 80% (w/w) sulphuric acid at 180-190°C. (The bromopseudocumene had to be removed quickly or decomposition occurred.) On distillation a mixture of 3-bromo-(80%) and 5-bromo-(20%) pseudocumene was obtained. (Analyses on column (8) and infrared. Total yield 60%.)

As the 5-bromopseudocumene is a solid at room temperature (m.p. 70°C) and the other isomers are liquids, it was found possible to purify the product by low temperature fractional recrystallization. The purification proceeded through three stages. First, the mixture was cooled until crystals formed which, when filtered off, did not melt on warming. This reduced the impurity content of the mother liquor to 12%. Secondly, the addition of pentane allowed the process to be repeated until the impurity was down to 7%. At this stage the crystals melted at room temperature and began to contain less impurity than the mother liquor. Successive recrystallizations then gave a fraction containing less than 1.3% 5-bromopseudocumene.

5-Bromopseudocumene was prepared by the method of Smith and Kiess.<sup>50</sup> Pseudocumene-5-sulphonic acid was prepared by the method of Smith and Moyle<sup>51</sup> and then brominated with bromine in 50% aqueous (v/v) hydrochloric acid. Extraction of the ether-soluble fraction and several recrystallizations from ethanol yielded 5-bromopseudocumene (m.p. 69-70°C. Yield 10%) pure by column (8) and infrared, and identical with the other reaction product in the synthesis of 3-bromopseudocumene.

6-Bromopseudocumene was prepared by the method of Carpenter and Easter.<sup>52</sup> Pseudocumene was nitrated using  $\text{HNO}_3/\text{H}_2\text{SO}_4$  and after distillation and recrystallization from methanol, 5-nitropseudocumene (m.p. 69.5-70.5°C. Yield 25%) was obtained and appeared pure by columns (4) and (8), and infrared.

5-Pseudocumidene hydrochloride was obtained by reduction of the nitropseudocumene with iron powder in aqueous ethanol and hydrochloric acid. The product was recrystallized from ethanol/ethyl acetate and a small portion was converted to amine and appeared to be pure by column (5). (Yield 72%)

The amine hydrochloride was brominated in a mixture of acetic acid and 30% aqueous hydrochloric acid and the product washed with water and benzene to give 6-bromo-5-

pseudocumene hydrochloride (Yield 90%), pure by N.M.R. (using trifluoroacetic acid as solvent) and infrared. G.L.C. analyses of the amine, obtained by treating the hydrochloride with base, showed product compositions that varied with the conditions of conversion.

The hydrochloride was dissolved in a mixture of tetrahydrofuran and aqueous hydrochloric acid and diazotised with aqueous sodium nitrite. This solution was added to a cold solution of alkaline stannous chloride and the product obtained by steam distillation and distillation through a Nester-Faust spinning-band column was pure on column (5) and infrared. (Yield 40%)

Bromomesitylene (Fluka "purum" grade) was analysed on column (8), N.M.R., and infrared. No impurities could be detected.

Bromoprehnitene was obtained by bromination of prehnitene (K & K), which had been shown to be isomer free by G.L.C., N.M.R., and infrared. The reaction was carried out at 0°C using bromine in chloroform. After distillation the product was shown to contain less than 2% of prehnitene and dibromoprehnitene by G.L.C., and N.M.R. N.M.R. showed there was less than 2% of either bromodurene or bromo-isodurene present. Column (6) showed no bromo-isodurene and a variable amount



(1-5%) of bromodurene which seemed to be forming on the column, or in the injector.

Bromo-isodurene was prepared by chloromethylation of bromomesitylene and partial reduction of the product. This route was chosen because no pure isodurene or mesitylene was available. Di-(chloromethyl)-ether (16.6g) was dissolved in trifluoroacetic acid (50ml) and bromomesitylene (28.0g) added. The mixture was kept at 50-60°C overnight and then poured into 250mls of saturated sodium carbonate solution. After extraction with ether and washing with water the ethereal solution was dried over anhydrous magnesium sulphate and the ether evaporated leaving 36g of crude solid product. An attempt to recrystallize this from ethanol converted 30% into 3-bromo-2,4,6-trimethylbenzyl ethyl ether. (N.M.R. and mass spectral analyses.) Dichloromethylated product and its corresponding ether were also detected and the mass spectrum showed about 1% of dibromomesitylene. (The reactivity of the bromo-chloromethyl-mesitylene towards ethanol was rechecked and it was found, as before, that no reaction could be detected after several hours at room temperature, but that at reflux 30% conversion was obtained in about ten minutes.) G.L.C. analysis was not possible because of decomposition of the material

at high temperatures. The mixture obtained from the recrystallization was then distilled under reduced pressure and fractions boiling at 140-150, 150-170, and 170-200°C at 6mm were obtained.

2.7g of the first fraction were dissolved in cold ethanol (11ml) containing triethylamine (1.1g) and Raney nickel (W2, 0.1).<sup>53</sup> This mixture absorbed 175ml of hydrogen in 40 minutes and N.M.R. showed the reaction had gone almost to completion. The mixture was filtered, the solvent evaporated off, and then the residue was eluted through a silica gel/alumina column with pentane, before being fractionally distilled. A fraction of bromo-isodurene (0.79g) was obtained showing 1-1.5% bromoprehnitene and less than 1% of total other impurities by a combination of column (6) and N.M.R. analyses.

Bromodurene was prepared by bromination of durene (B.D.H.) which was found to be isomer-free by G.L.C. and N.M.R. analyses. The brominating reagent was bromine in chloroform at 0°C. After fractional distillation the final product contained 2.5% dibromodurene and less than 1% durene. N.M.R. showed clearly less than 1% bromoprehnitene in spite of a variable 10-20% appearing in G.L.C. No bromo-isodurene was observed.

(v) Preparation of the Tritiated Hydrocarbons

The general method for the conversion of the haloaromatics into Grignard reagents was as follows. The halo aromatic was dissolved in 5 volumes of dry ether and dried over 5A molecular sieve. A three-necked flask was fitted with a double surface condenser and drying tube, a teflon blade stirrer and oil seal, and a pressure-equalizing dropping funnel connected to a nitrogen line via a sodium hydroxide drying tube, a sulphuric acid bubbler and (if diethyl ether was being used) another bubbler containing dry ether to reduce solvent loss during the reaction.

A 10% excess of magnesium turnings (Riedel de Haen) and a drop of dibromoethane was used to form the Grignard reagent. As these halides are deactivated it was often necessary to warm the reaction mixture. However, the more highly substituted compounds reacted quite readily, suggesting that the relief of steric strain was more than compensating for their electronic deactivation. No difficulties were encountered in forming the Grignards from chlorides or iodides and the only significant amount of dimerization occurred with p-bromotoluene. If the reaction did not start in diethyl ether some tetrahydrofuran was added to the reaction vessel. It was desirable to use a minimum amount of tetrahydrofuran; its higher

boiling point makes its removal more difficult than diethyl ether, and its solubility in water makes extraction more difficult.

The Grignard reagent was then decomposed with the theoretical amount of tritiated water. Usually a 10mc/ml activity was used, but if only a small amount of the aryl halide was available then a 20 mc/ml solution would be used and a quantity of the appropriate unlabelled aromatic hydrocarbon added. The solution was stirred for half an hour and then excess water added. The precipitated magnesium salts were dissolved in saturated ammonium chloride solution and extracted with pentane. The combined extracts were washed and dried over magnesium sulphate before being distilled. It was found that the last traces of ether could be removed by washing with concentrated hydrochloric acid, but this was not used for the more reactive compounds in case hydrogen exchange occurred.

The reaction product was analysed by G.L.C. and infrared. It was then stored in the dark. If colour developed during storage, samples were redistilled before use.

Samples of 6- $H^3$ -pentamethyl benzene and 3- $H^3$ -o-xylene were available from work by Mr. B.N. McMaster and Dr. G.J. Wright respectively.<sup>55</sup>

(B) Measurement of Rate Constants for Hydrogen Exchange

(i) Materials

Trifluoroacetic acid (Fluka 'purum') was distilled through a 2ft precision-bore vigreux column, first off silver oxide and then off sulphuric acid. (Riedel de Haen, A.R. grade containing less than 0.00006% Cl)

Scintillator: p-terphenyl (Nuclear Enterprises, 10g) and 1,4-bis-(2-(5-phenyloxazolyl))-benzene (Nuclear Enterprises, 0.025g) were dissolved in toluene (B.D.H. A/R grade 2.5 litres).<sup>56</sup>

(ii) Instruments

Scintillation counts were made on an I.D.L. Model (6012) Liquid Scintillation Counter. This is a dual channel coincidence counter with single channel output to a scalar.

Runs at 70.0°C were conducted in a waterbath with 400W base heater and a 1.5KW heater switched by a Jackson thermoregulator via a Gallenkamp relay. For runs at less than 20°C a Townsend and Mercer 'Minus Seventy' coldbath was used. Measurements at intermediate temperatures were made in a bath controlled by a 1.5KW 'Tempunit' (Tecam).

### (iii) Method

The method used was basically that developed by Eaborn and his co-workers.<sup>57</sup> About 40mg of tritiated aromatic was dissolved in 10ml of trifluoroacetic acid and placed in a thermostat bath. Aliquots (1ml) were removed at known times, quenched in a solution of 1% NaOH (100ml), and extracted into scintillator solution (10ml). These were then washed with water (100ml), dried over anhydrous  $\text{MgSO}_4$ , and a 4ml portion measured out accurately for counting. Eight such aliquots were usually taken per run and counted on the same day.

If the run was slow enough to allow ampoules to be used, these were filled with aliquots of reaction mixture using a glass pipette controlled by a 5ml syringe (connected by a piece of rubber tubing). The ampoules were kept in an icebath until sealed. (At least 25% air space was required to allow for expansion at 70°C.) The ampoules were held in a metal clip rack in the bath during the run and when required were removed, washed with ether and water, scratched with a glass-knife, and broken with a brass rod in a long-necked, conical, stoppered flask (250ml) containing alkali and scintillator.

For fast runs 10ml of trifluoroacetic acid were brought to bath temperature in a stoppered, volumetric flask. The tritiated hydrocarbon was added as a liquid (solids

were dissolved in two drops of toluene) and the flask stoppered, shaken, and replaced in the bath. A syringe with a coarse needle was used to extract aliquots and expel them quickly into separatory funnels containing the alkali and scintillator solutions.

#### (iv) Sources of Error

##### (1) Volumetric

Three precise volumetric measurements were required. The measurement of the 10ml of scintillator solution and the 4ml counting aliquots were made using constant volume pipettes closed by a stopcock. These were shown to give aliquots of standard deviation less than 0.2%.

The aliquots of reaction mixture were either measured first into glass ampoules, using glass pipettes (1ml), before being placed in the bath, or were withdrawn from a flask by a syringe (1ml), and immediately quenched. The latter method had to be used for fast reactions and did not appear to give significantly greater scatter in the kinetic runs. The standard error of this measurement was about 1%.

##### (2) Counting Statistics, Geometry, and Fluorescence

A Poisson distribution for counting statistics was assumed, and at least 10,000 counts made per sample

(usually 20,000). The standard deviation of the count should then be less than 1%. The sample bottles used had screw-caps and if these were noticeably loose the count was 1% too low. The sample bottles were cleaned before counting and the self-centring device employed by the counter appeared to eliminate errors of position. Keeping the samples in a darkened room during counting reduced fluorescence which appeared to become negligible after 3-4 minutes in the dark.

### (3) Quenching Effects

#### (a) Solvents

Traces of ketones and halocarbons have significant quenching effects on the scintillator system employed (p-Terphenyl and POPOP).<sup>58</sup> For example, 0.3% acetone impurity reduced the count by 55%. Dilute mineral acids and alkali had no effect; neither did water, pentane, or ether. 0.3% methanol reduced the count by 2%. Trifluoroacetic acid also had a strong quenching action, but this was reversed by washing with dilute alkali.

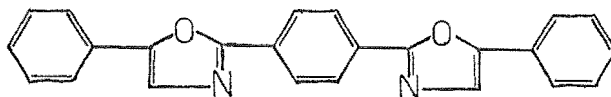
Accordingly, glassware was washed with ether and benzene, rather than acetone.

#### (b) Reaction Products

Some samples turned the scintillator yellow and gave anomalously low counts. The occurrence of these did not



appear to depend on particular runs. It was found that the count could be increased by up to 150% and the colour removed by shaking vigorously with 40% (v/v) aqueous hydrochloric acid, and then washing with dilute sodium hydroxide and water. Counts of normal samples were unchanged by this procedure. Although this treatment might be expected to remove some of the POPOP by protonation, the count was unchanged by addition of a little POPOP to these solutions.



1,4-bis-(2-(5-phenyloxazolyl))-benzene ('POPOP')

No impurity could be detected in the yellow solutions by N.M.R.

In some cases attempts were made to calibrate the efficiencies of the scintillator solutions by addition of a known amount of a solution of known activity but this method involved considerably more labour, and usually did not improve the data.

#### (4) Instrumentation

##### (a) Photomultiplier Tubes

After a period of use the counting efficiency of the counter as measured by a standard sample showed a charac-

teristic 'warm-up' curve. The counting efficiency increased with the activity of the counted sample and required about an hour to reach its maximum value if the machine had been on, but not counting, for some time. The decay curve was somewhat slower. The change involved was up to 20% of the normal efficiency and was tentatively ascribed to the photomultiplier tubes.

To overcome this an initial warm-up period was allowed, the order of counting of samples for each run was randomised and a standard sample was counted periodically during the counting of the run. A plot of efficiency against time was then constructed allowing corrections to be made.

(b) Time Constants of Electronics

The coincidence discriminating counter used has several relevant time constants. The 'relaxation' time of the entire counting assembly was about 3 micro-seconds. The 'coincidence discrimination' time within which pulses were considered coincident was about 0.1 micro-second. A 'delay' time of 1 micro-second could be imposed on one input, thus ensuring only 'accidental' coincidences were counted as a check procedure. These times were measured using a double-pulse generator and oscilloscope. A correction for relaxation time was made by the least squares program, OLS, when the count-rates were being computed. (See page 49.)

(5) Time

As pentamethylbenzene reacts some one hundred and fifty million times faster than benzene it was necessary to use rather varied means of measuring the time at which points were taken. For the very fast runs a "Minerva" stopwatch calibrated in tenths of a second was used, but the reading error was at least half a second.

(6) Temperature

Standard temperatures were determined using mercury in glass thermometers calibrated in tenths of a degree and standardised by the Dominion Physical Laboratory. The bath at  $70.0^{\circ}\text{C}$  maintained its temperature to  $\pm 0.03^{\circ}\text{C}$ . The "Tempunit" maintained  $\pm 0.05^{\circ}\text{C}$ . The "Minus Seventy" coldbath maintained  $\pm 0.1^{\circ}\text{C}$ .

## DATA PROCESSING

### (A) Computers

An IBM System 360 computer using Fortran 44 programs was used to perform least squares analyses. Output was provided in card form to enable graphs to be plotted on an IBM 1620 computer with a 1627 Plotter attachment.

### (B) Programs

#### (i) Organic Least Squares (OLS)

A general least squares procedure was used to obtain the rate-constants directly from the exponential decay curve of the radio-activity of the tritiated samples.

#### (1) Input Required

Data was supplied in the following form. Observed count, count time, background count-rate, and reaction time for each point of a run. For each run an approximate rate constant and initial count-rate were also supplied.

#### (2) Preparation of Data

The program converted the reaction time to seconds from the optional hours, minutes, and seconds input. It calculated the count-rate for each point making corrections for background, and assuming a relaxation time of

3 micro-seconds for the counter. (see page 45) Each point was weighted according to the equation:

$$\sigma = \sqrt{C_R/t_c + W^2 \cdot C_R^2}$$

Here  $C_R$  is the count-rate,  $t_c$  is the count time, and  $W$  is a constant. The first term represents the Poisson distribution error for the measurement of the count. The second represents a constant percentage error in obtaining the sample.  $W$  was usually taken as 0.014.

### (3) Screening of Data

Occasionally a point will lie well off the line. This may be due to spillage, contamination leading to catalysis or quenching, or to errors in preparing the data. These points should clearly be left out of the analysis. After three cycles of refinement the deviations of points from the line were tested before each of the three subsequent cycles. Any points lying further than 3.0 standard deviations from the line were given zero weight and the refinement continued allowing such points to re-enter the analysis if they passed the test at a later cycle.

Some runs may show a greater scatter than others, and this will be reflected in a high value for the estimated standard error of a point of unit weight if the weighting scheme is not adjusted. A good weighting

scheme is necessary for true predictions of parameters and errors, and is essential if a realistic decision on whether to ignore a data point is to be made.

To allow for an incorrect initial estimate of  $W$  (and hence the weighting scheme) the program tested discarded points to see if they lay within  $6.0\sigma$  of the line. If there were any such points, the analysis was repeated with  $W^2$  doubled in value. If necessary  $W^2$  could be doubled again. A complete set of possible weighting schemes is then available so that a decision on the homogeneity of the scatter of a run can be made, and parameter estimates using an appropriate value of  $W$  are available.

#### (4) Output

The program prints out the parameters and estimated standard deviations, the corrected observed count-rates with their deviations from the observed values, and the estimated standard error of a point of unit weight (which should be close to unity for a large number of observations and the correct weighting scheme). Computation time is 20 seconds to one minute depending on how many weighting schemes are tried.

#### (5) General Least Squares Method

This program was adapted from ORGLS<sup>59</sup>, and uses the

general least squares refinement method<sup>60</sup> to adjust the values of the parameters of an arbitrary function. The adjustment proceeds so as to minimise the sum of the squares of the differences between the dependent variable values observed experimentally and the corresponding values calculated from the independent variables. A Taylor expansion about a point in parameter space is performed to calculate the adjustments required for the parameters assuming linearity for small changes (i.e. higher order terms vanish). The new point is used to calculate further adjustments and the process repeated until convergence is reached. For very non-linear functions it may be essential to start with parameters very close to the true values.

The general least squares method has the great advantage of working for any function but the disadvantage of requiring approximate values of the parameters and the complication of being an iterative process.

The function used was  $YCALC = P(1) \cdot \exp(-P(2) \cdot T) + P(3)$  where  $P(i)$  are the parameters which may be either varied or held constant. For the analysis of the radio-activity of the aliquot of tritiated hydrocarbon taken at time  $t$  from the reaction mixture,  $P(3)$  is the count-rate when  $T$  is large,  $(P(1) + P(3))$  is the count-rate at  $t = 0$ ,  $P(2)$  is the rate-constant and  $YCALC$  is the count-rate at  $t = T$ .

(The same equation may be used for following 'appearance of product' kinetics.)

### (ii) Stepwise Multiple Regression (STEPR)

This program was taken from the IBM Scientific Subroutines Package<sup>61</sup> with few modifications. A regression analysis is performed on a linear function by a stepwise procedure, adding one independent variable at a time. The result is a sequence of least squares fits of the observed data to the function  $Y = \sum_{i=1}^N B_i \cdot X_i$  where  $B_i$  are the regression coefficients (i), and  $X_i$  are the independent variables chosen in order to give the best fit at each step as  $N_s$  increases by unit increments to the number of variables required. It is thus possible to assess the significance of each independent variable brought into the analysis.<sup>62,63</sup>

### (iii) Graph Plotting Subroutines

Two subroutines (PLOTQ calls QGRAF) were written to plot the result of a least squares regression. When STEPR completed an analysis PLOTQ was called and read title and dimension defining cards for the graph. It then called QGRAF which used PLOTA<sup>64</sup> subroutines to construct condensed output suitable for direct use by the IBM 1620 and PLOTTER. The resultant graph fits a



quarto page, is accurate to 0.01in, has titles centred, and can plot points, a straight line, or a curve. 1620 input is usually four cards with drawing-time about two minutes per graph.

A small 'stand-alone' program was also written to accept all data for QGRAF in card form. Six cards is the complete input required for a graph of eight points and a straight line.

(C) Example of Use of OLS

The following is an example of the way in which the rate-constants for detritiation were derived from the raw data.

(i) Input Data

4-H<sup>3</sup>-hemimellitene (20mg) was placed in trifluoroacetic acid (10ml, 70.0°C) in a 10ml flask which was stoppered and shaken. Nine aliquots were taken as described earlier (page 42), and the following results were punched on cards for processing by OLS.

<u>Aliquot</u>	<u>Time Quenched</u>			<u>Count</u>	<u>Count Time</u>	<u>Background</u>
	(hrs)	(min)	(sec)		(sec)	<u>Count Rate (c/s)</u>
1		0	0	35326	10	0.84
2		1	08	122779	40	0.84
3		2	21	26697	10	0.84
4		3	34	21850	10	0.84
5		5	15	35140	20	0.84
6		7	33	37529	30	0.84
7		11	28	30026	40	0.84
8		17	08	14630	40	0.84
9	12	35	-	5380	100	0.84

Computer Output Produced by OLS

A.L. WILKINSON HYDROGEN EXCHANGE KINETICS 4-T-HEMIMELLITENE

RUN 50

NUMBER OF CYCLES IN THIS JOB IS 6

NUMBER OF PARAMETERS TO BE VARIED IS 3

NUMBER OF INDEPENDENT VARIABLES PER OBSERVATION IS 5

VALUE OF WEIGHTING CONSTANT IS 0.002

DERIVATIVES PROGRAMMED BY USER

WEIGHTS TO BE SUPPLIED BY USER

PARAMETERS TO BE READ AS INPUT DATA

CORRECTED PARAMETERS NOT TO BE SAVED FOR LATER USE

NUMBER OF PARAMETERS READ IS 3

NUMBER OF OBSERVATIONS IS 9

INPUT DATA

I	P(I)	KI(I)	DP(I)
1	0.3532E 04	1	0.0
2	0.2300E-02	1	0.0
3	0.0	1	0.0

AGREEMENT FACTORS BASED ON PARAMETERS BEFORE CYCLE 3

SUM(W\*(O-C)\*\*2) IS 0.723E 00

SQRTF(SUM(W\*(O-C)\*\*2)/(NO-NV)) IS 0.3470

PARAMETERS AFTER LEAST SQUARES CYCLE 3

	OLD	CHANGE	NEW	ERROR
1	0.3580E 04	-.1387E-02	0.3580E 04	0.3062E 02
2	0.2374E-02	-.1230E-08	0.2374E-02	0.1888E-04
3	0.5297E 02	-.2937E-05	0.5297E 02	0.8592E 00

ESTIMATED AGREEMENT FACTORS BASED ON PARAMETERS AFTER CYCLE 3

SUM(W\*(O-C)\*\*2) IS 0.723E 00

SQRTF(SUM(W\*(O-C)\*\*2)/(NO-NV)) IS 0.3470

CALCULATED Y BASED ON PARAMETERS BEFORE CYCLE 4

Y(OBS)	Y(CALC)	OBS-CALC	SIG(O)	(O-C)/ SIG(O)	X(1)	CT.TIME	BKGRD
4097.02 ?							
3097.02	3099.01	-1.98	138.78	-0.01	68.	40.0	0.84
3569.39	3632.68	-63.28	160.74	-0.39	0.	10.0	0.84
2690.32	2614.32	76.00	121.42	0.62	141.	10.0	0.84
2198.52	2206.76	-8.23	99.43	-0.08	214.	10.0	0.84
1765.44	1747.57	17.87	79.51	0.22	315.	20.0	0.84
1254.83	1274.15	-19.32	56.48	-0.34	453.	30.0	0.84
751.50	751.98	-0.48	33.88	-0.01	688.	40.0	0.84
365.31	364.80	0.50	16.61	0.03	1028.	40.0	0.84
52.96	52.96	0.00	2.47	0.00	45300.	100.0	0.84

SUBROUTINE TEST INDICATES THAT JOB IS TO BE TERMINATED FOR  
REASON 1

CORRELATION MATRIX

1	1.0000	0.7310	0.0012
2	0.0	1.0000	0.1178
3	0.0	0.0	1.0000

(ii) Explanation of Output

The number of independent variables, shown as 5, includes the three input variables expressing time in the optional hours, minutes, and seconds, the background count-rate, the count time, and an optional variable for an estimated standard error for each observation. (The last is redundant here because these weights are calculated by the program as described previously. The weighting constant of 0.002 is  $W^2$  (page 49).)

KI(I) = 1 shows that the  $I^{\text{th}}$  parameter, P(I), is to be varied. DP(I) is the increment to be used if parameter derivatives are to be obtained numerically, and is redundant here.

<u>Fortran Symbol</u>	<u>Algebraic Equivalent</u>
2.OE-02	$2 \times 10^{-2}$
W*(O-C)**2	$W.(O-C)^2$
<u>Symbol</u>	<u>Meaning</u>
NO	number of observations
NV	number of parameters varied = 3
W	weight = $1/\sigma^2$
ERROR	estimated standard errors of parameter estimates
Y(OBS), OBS, O	observed count-rate (after corrections for background and relaxation time)
YCALC, CALC, C	calculated count-rate (from quenching time and parameters)

<u>Symbol</u>	<u>Meaning</u>
SIG(O)	standard error of observed count-rate
X(I)	quenching time (sec)
CT.TIME	count time (sec)
BKGRD	background count-rate (c/s)
REASON 1	the refinement has converged and no points have been discarded
REASON 2	the refinement has converged and there are no discarded points close enough to the predicted values to warrant increasing $W^2$
REASON 3	$W^2$ has been doubled twice.

$\text{SQRTF}(\text{SUM}(W*(O-C)**2)/(\text{NO}-\text{NV}))$  is the estimated standard deviation of a point of unit weight. The value here of 0.347 is exceptionally and fortuitously low for this value of  $W^2$ .

The effect of cycle 3 on the parameters is shown and the changes are very small. In conjunction with the lack of change in the agreement factors this shows that convergence has been achieved.

The Correlation Matrix consists of the estimated covariances of the parameters. ( $\rho_{ij} \leq 1$ )

(D) Example of Use of STEPR(i) Input for STEPR

The use of program STEPR is illustrated by the simple problem of finding the least squares values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  from Arrhenius plots. For 4-H<sup>3</sup>-isodurene the following measurements were made and punched on cards as input for STEPR.

$k \times 10^3$ (sec <sup>-1</sup> )	$\sigma_k \times 10^3^a$ (sec <sup>-1</sup> )	$T$ (°C)
3.21	0.16	13.1
4.17	0.11	16.2
14.20	0.70	30.0
29.70	0.90	40.0

(a) Estimated by OLS, see Table 2.

A preliminary subroutine (DATA) was used to calculate the following variables.

$$x_1 = k$$

$$x_2 = \sigma_k$$

$$x_3 = T_{\text{ABS}} = T_{\text{OC}} + 273.15$$

$$x_4 = 1/T_{\text{ABS}} = 1/x_3$$

$$x_5 = R \cdot \log_e(kh/kT) = 1.9862 \log_e(x_1 \cdot x_4 / (2.0836 \times 10^{10}))$$

$$x_6 = RT \log_e(kh/kT) = x_3 \cdot x_5$$

The regression analysis of  $x_5$  on  $x_4$  yields slope  $-\Delta H^\ddagger$  and intercept  $\Delta S^\ddagger$  while the analysis of  $x_6$  on  $x_3$  yields slope  $\Delta S^\ddagger$  and intercept  $-\Delta H^\ddagger$ . These two analyses were performed as 'selections' one and two respectively, and the computer output is reproduced on the following pages. This problem in a sense is a trivial case for the stepwise procedure, as only one variable needs to be introduced in each selection.

Graph dimensions were also supplied for the attached QGRAF subroutine which used the table of residuals calculated by STEPR to construct the graphs shown in Appendix A.



Example of Output Produced by STEPR

STEP-WISE MULTIPLE REGRESSION.....T-ISOD

NUMBER OF OBSERVATIONS 4

NUMBER OF VARIABLES 6

NUMBER OF SELECTIONS 2

CONSTANT TO LIMIT VARIABLES 0.0

VARIABLE NO.	MEAN	STANDARD DEVIATION
1	0.12770E-01	0.12295E-01
2	0.45500E-03	0.38388E-03
3	0.29797E 03	0.12502E 02
4	0.33604E-02	0.13971E-03
5	-0.67944E 02	0.19903E 01
6	-0.20227E 05	0.25156E 03

CORRELATION MATRIX

ROW 1

1.00000	0.95773	0.97484	-0.96994	0.96672	-0.98093
---------	---------	---------	----------	---------	----------

ROW 2

0.95773	1.00000	0.98598	-0.98576	0.98748	-0.98021
---------	---------	---------	----------	---------	----------

ROW 3

0.97484	0.98598	1.00000	-0.99978	0.99939	-0.99916
---------	---------	---------	----------	---------	----------

ROW 4

-0.96994	-0.98576	-0.99978	1.00000	-0.99985	0.999834
----------	----------	----------	---------	----------	----------

ROW 5

0.96672	0.98748	0.99939	-0.99985	1.00000	-0.99724
---------	---------	---------	----------	---------	----------

ROW 6

-0.98093	-0.98021	-0.99916	0.99834	-0.99724	1.00000
----------	----------	----------	---------	----------	---------

SELECTION..... 1

DEPENDENT VARIABLE..... 5

NUMBER OF VARIABLES FORCED..... 1

NUMBER OF VARIABLES DELETED... 4

STEP 1

VARIABLE ENTERED..... 4

(FORCED VARIABLE)

SUM OF SQUARES REDUCED IN THIS STEP.... 0.1188E 02

PROPORTION REDUCED IN THIS STEP..... 1.000

CUMULATIVE SUM OF SQUARES REDUCED..... 0.118798E 02

CUMULATIVE PROPORTION REDUCED..... 0.9997 OF

0.118833E 02

FOR 1 VARIABLES ENTERED

MULTIPLE CORRELATION COEFFICIENT... 1.000

(ADJUSTED FOR D.F.).....9999E 00

F-VALUE FOR ANALYSIS OF VARIANCE... 6764.527

STANDARD ERROR OF ESTIMATE.....4191E-01

(ADJUSTED FOR D.F.).....4191E-01

VARIABLE NUMBER	REGRESSION COEFFICIENT	STD. ERROR OF REG. COEFF.	COMPUTED T-VALUE
4	-0.14243E 05	0.17318E 03	-0.8225E 02
INTERCEPT	-0.20080E 02		

SELECTION..... 1

## TABLE OF RESIDUALS

CASE NO.	Y VALUE	Y ESTIMATE	RESIDUAL
1	-0.69333E 02	-0.69306E 02	-0.27039E-01
2	-0.69831E 02	-0.69839E 02	0.78125E-02
3	-0.65591E 02	-0.65565E 02	-0.25925E-01
4	-0.67020E 02	-0.67065E 02	0.45135E-01

SELECTION..... 2

DEPENDENT VARIABLE..... 6

NUMBER OF VARIABLES FORCED.... 1

NUMBER OF VARIABLES DELETED... 8

STEP 1

VARIABLE ENTERED..... 3

(FORCED VARIABLE)

SUM OF SQUARES REDUCED IN THIS STEP.... 0.1895E 06

PROPORTION REDUCED IN THIS STEP..... 0.998

CUMULATIVE SUM OF SQUARES REDUCED..... 0.189528E 06

CUMULATIVE PROPORTION REDUCED..... 0.9983 OF

0.189848E 06

FOR 1 VARIABLES ENTERED

MULTIPLE CORRELATION COEFFICIENT... 0.999

(ADJUSTED FOR D.F.).....9992E 00

F-VALUE FOR ANALYSIS OF VARIANCE... 1187.335

STANDARD ERROR OF ESTIMATE.....1263E 02

(ADJUSTED FOR D.F.).....1263E 02

VARIABLE NUMBER	REGRESSION COEFFICIENT	STD.ERROR OF REG. COEFF.	COMPUTED T-VALUE
3	-0.20104E 02	0.58344E 00	-0.3446E 02
INTERCEPT	-0.14236E 05		
SELECTION..... 2			

## TABLE OF RESIDUALS

CASE NO.	Y VALUE	Y ESTIMATE	RESIDUAL
1	-0.20062E 05	-0.20053E 05	-0.80234E 01
2	-0.19989E 05	-0.19991E 05	0.19609E 01
3	-0.20540E 05	-0.20532E 05	-0.77578E 01
4	-0.20317E 05	-0.20331E 05	0.13805E 02

(ii) Explanation of STEPR Output

The regression method is the abbreviated Doolittle Method,<sup>62</sup> and constructs a correlation matrix containing as many independent variables as the user may wish to test. From these a 'selection' is made which must contain fewer than (n-1) variables if there are n observations. The selected variables can be divided into two categories, forced, and unforced. The step-wise analysis then proceeds, selecting and evaluating one variable at a time until the first category has been exhausted. Variables from the second category then become eligible for entry into the regression, which continues until the proportion of sums of squares reduced in a step falls below a value supplied and designated 'CONSTANT TO LIMIT VARIABLES'. If, as here, this is zero, the analysis is completed when all the selected variables have entered the regression. As many different selections may be made as desired to test alternative hypotheses, and there is no need to recalculate the correlation matrix each time. Within the categories, variables are chosen in an order defined by their ability to reduce the deviations from the regression line.

CORRELATION MATRIX - the elements  $C_{jk}$  are of the form:

$$C_{jk} = (a_{jk}) / (a_{jj} \cdot a_{kk})^{\frac{1}{2}}$$

where  $a_{jk} = \sum_0^n (x_{j0} \cdot x_{k0} - \bar{x}_j \cdot \bar{x}_k)$ , and the sum is taken over the n observations.

The 'MULTIPLE CORRELATION COEFFICIENT' has the value

$R = \sqrt{P_{\text{CUM}}}$  where  $P_{\text{CUM}}$  is the cumulative proportion of squares reduced.

The 'ADJUSTMENT FOR DEGREES OF FREEDOM' takes the form:

$$R_c = \sqrt{1 - (1-R)^2(n-1)/(n-k)}$$

for  $k$  independent variables in regression.

'F-VALUE' takes the form:

$$F = (S_{\text{CUM}}/k) / (S_{\text{CUM}}^1/(n-k-1))$$

where  $S_{\text{CUM}}^1$  is the residual sum of squares after  $k$  variables have been entered. This value can be used in the F-test for significance of the correlation.

The 'STANDARD ERROR OF ESTIMATE' is calculated as

$$S = \sqrt{S_{\text{CUM}}^1/(n-k-1)}$$

The value 'ADJUSTED FOR DEGREES OF FREEDOM' is

$$S_c = S \sqrt{n-1/n-k}$$

The 'REGRESSION COEFFICIENT' of 'VARIABLE 4' corresponds to  $\Delta H^\ddagger$ .

The 'T-VALUE' calculated as the ratio of the regression coefficient to its error, can be used to test the significance of each variable.

The 'INTERCEPT' corresponds to  $\Delta S^\ddagger$ .

## RESULTS

### (A) Rates of Detritiation

Eighty-four kinetic runs were performed on the tritiated polymethylbenzenes and results are shown in the following tables. Table 2 lists the rate-constant and standard error for each run as calculated by OLS (page 48). For each compound rate-constants, estimated standard errors of the means, and values previously reported in the literature are shown in Table 3.

### Temperature Extrapolation

The values for the rate-constants for 6-H<sup>3</sup>-pentamethylbenzene and 4-H<sup>3</sup>-isodurene at 70.0°C were obtained by extrapolation from temperature ranges of 10-30°C and 13-40°C respectively. For comparison, Arrhenius plots were also determined for 3- and 5-H<sup>3</sup>-pseudocumenes. The regression line of the variable  $R \ln(kh/kT)$  (where  $R$ ,  $h$ ,  $k$ , are the gas, Plank's and Boltzmann's constants, respectively,  $T$  is the absolute temperature, and  $k$  is the rate-constant) on the variable  $1/T$  yields a line of slope  $\Delta H^\ddagger$  and intercept  $\Delta S^\ddagger$  if the absolute theory is assumed. The estimated standard errors for  $\Delta H^\ddagger$  and for the deviation of the experimental points from the best line are also calculated.

From the absolute rate theory the simplified equation  $k = (kT/h) \cdot e^{-(\Delta H^\ddagger - T\Delta S^\ddagger)/RT}$  may then be used to calculate the rate-constant at 70.0°C. The standard error of this prediction may be regarded as due to the propagation of two independent errors.<sup>65</sup>

### (1) Error of $\bar{y}$

If the line  $y = mx + c$  is being fitted to a set of observations,  $y_i$  ( $i = 1, \dots, n$ ), and their set of corresponding independent variables,  $x_i$  ( $i = 1, \dots, n$ ), then the least squares process adjusts  $c$  so that the line passes through  $(\bar{x}, \bar{y})$  where  $\bar{x}$  is the mean value of  $x_i$  ( $\frac{1}{n} \sum_{i=1}^n x_i$ ),

and  $\bar{y}$  is the mean value of  $y_i$ . If the experimental standard error of the points is  $\sigma_y$  (the error in the measurement of  $x$  is small) then the standard error of the estimate of  $\bar{y}$  is  $(\sigma_y^2/n)^{\frac{1}{2}}$ .

### (2) Error of $m$

When the calculated value of  $m$  for the set of  $n$  observations is used to predict a value  $y_r$  for a given  $x_r$  then the error due to the extrapolation is  $\sigma_m |\bar{x} - x_r|$  where  $\sigma_m$  is the standard error of the estimate of the slope,  $(m)$ .

The resultant standard error of the predicted value of  $y$  ( $y_r = \bar{y} + m(x_r - \bar{x})$ ) is given by



$$\sigma_{y_r} = \sigma_y^2/n + \sigma_m^2(\bar{x} - x_r)^2$$

e.g. for the pentamethylbenzene calculation  $n = 5$ ,

$\sigma_y = 0.0728$ ,  $\sigma_m = \sigma_{\Delta H^\ddagger} = 268$ ,  $\bar{x} = 0.003456$ . Hence for

$x_r = 1/343.15 \text{ degrees}^{-1}$ ,  $\sigma_{R.\ln(k_{343.15})} = 0.142$ , and so

$$\sigma_{k_{343.15}} = 0.52 \times 10^{-1} (\text{sec}^{-1}).$$

Values of the enthalpies and entropies of activation are shown in Table 4. The Arrhenius plots are shown in Appendix A.

TABLE 2

Rate-Constants For Detritiation of Polymethylbenzenes in  
Trifluoroacetic Acid

<u>Compound</u>	<u>k</u>	<u><math>\frac{a}{k}</math></u>	<u>(sec<sup>-1</sup>)</u>	<u><math>\frac{T^b}{(^{\circ}\text{C})}</math></u>
H <sup>3</sup> -benzene	( 3.68	0.55	) x 10 <sup>-9</sup>	
	( 6.17	0.71	) x 10 <sup>-9</sup>	
o-H <sup>3</sup> -toluene	( 1.883	0.042	) x 10 <sup>-6</sup>	
	( 1.946	0.036	) x 10 <sup>-6</sup>	
	( 1.91	0.12	) x 10 <sup>-6</sup>	
m-H <sup>3</sup> -toluene	( 4.75	0.11	) x 10 <sup>-8</sup>	
	( 5.34	0.15	) x 10 <sup>-8</sup>	
	( 6.50	0.13	) x 10 <sup>-8</sup>	
	( 6.88	0.46	) x 10 <sup>-8</sup>	
p-H <sup>3</sup> -toluene	( 4.206	0.027	) x 10 <sup>-6</sup>	
	( 4.008	0.045	) x 10 <sup>-6</sup>	
	( 4.036	0.092	) x 10 <sup>-6</sup>	
	( 4.044	0.049	) x 10 <sup>-6</sup>	
	( 3.981	0.041	) x 10 <sup>-6</sup>	
	( 4.212	0.028	) x 10 <sup>-6</sup>	
	( 3.817	0.039	) x 10 <sup>-6</sup>	
	( 4.059	0.051	) x 10 <sup>-6</sup>	
3-H <sup>3</sup> -o-xylene	( 1.302	0.033	) x 10 <sup>-5</sup>	
	( 1.241	0.029	) x 10 <sup>-5</sup>	
	( 1.251	0.011	) x 10 <sup>-5</sup>	

a, b see page 73

TABLE 2 (continued)

Compound	<u>k</u>	<u><math>\sigma_k^a</math></u>	<u>(sec<sup>-1</sup>)</u>	<u><math>\frac{T^b}{(^{\circ}\text{C})}</math></u>
3-H <sup>3</sup> -o-xylene	( 1.388	0.025 )	x 10 <sup>-5</sup>	
(continued)	( 1.120	0.012 )	x 10 <sup>-5</sup>	
4-H <sup>3</sup> -o-xylene	( 1.857	0.015 )	x 10 <sup>-5</sup>	
	( 1.813	0.017 )	x 10 <sup>-5</sup>	
	( 1.846	0.019 )	x 10 <sup>-5</sup>	
	( 1.737	0.026 )	x 10 <sup>-5</sup>	
2-H <sup>3</sup> -m-xylene	( 3.72	0.09 )	x 10 <sup>-4</sup>	
	( 3.66	0.05 )	x 10 <sup>-4</sup>	
	( 3.58	0.09 )	x 10 <sup>-4</sup>	
4-H <sup>3</sup> -m-xylene	( 6.89	0.38 )	x 10 <sup>-4</sup>	
	( 7.64	0.09 )	x 10 <sup>-4</sup>	
5-H <sup>3</sup> -m-xylene	( 4.22	0.10 )	x 10 <sup>-7</sup>	
	( 4.39	0.14 )	x 10 <sup>-7</sup>	
	( 4.18	0.14 )	x 10 <sup>-7</sup>	
2-H <sup>3</sup> -p-xylene	( 1.393	0.018 )	x 10 <sup>-5</sup>	
	( 1.539	0.027 )	x 10 <sup>-5</sup>	
	( 1.607	0.016 )	x 10 <sup>-5</sup>	
	( 1.428	0.021 )	x 10 <sup>-5</sup>	
4-H <sup>3</sup> -hemimellitene	( 2.374	0.019 )	x 10 <sup>-3</sup>	
	( 2.479	0.050 )	x 10 <sup>-3</sup>	
	( 2.362	0.010 )	x 10 <sup>-3</sup>	
	( 2.371	0.020 )	x 10 <sup>-3</sup>	

TABLE 2 (continued)

<u>Compound</u>	<u>k</u>	<u><math>\sigma_k^a</math></u>	<u>(sec<sup>-1</sup>)</u>	<u><math>\frac{T^b}{(^{\circ}\text{C})}</math></u>
5-H <sup>3</sup> -hemimellitene	( 8.56	0.10 )	x 10 <sup>-5</sup>	
	( 7.59	0.06 )	x 10 <sup>-5</sup>	
	( 8.66	0.17 )	x 10 <sup>-5</sup>	
	( 8.10	0.10 )	x 10 <sup>-5</sup>	
3-H <sup>3</sup> -pseudocumene	( 1.601	0.049 )	x 10 <sup>-3</sup>	
	( 1.533	0.020 )	x 10 <sup>-3</sup>	
	( 1.547	0.030 )	x 10 <sup>-3</sup>	
	( 3.39	0.04 )	x 10 <sup>-4</sup>	50.0
	( 5.30	0.09 )	x 10 <sup>-5</sup>	29.8
5-H <sup>3</sup> -pseudocumene	( 2.70	0.08 )	x 10 <sup>-3</sup>	
	( 2.622	0.036 )	x 10 <sup>-3</sup>	
	( 2.789	0.028 )	x 10 <sup>-3</sup>	
	( 2.867	0.026 )	x 10 <sup>-3</sup>	
	( 2.726	0.035 )	x 10 <sup>-3</sup>	
	( 6.02	0.035 )	x 10 <sup>-4</sup>	50.0
	( 1.018	0.026 )	x 10 <sup>-4</sup>	29.8
6-H <sup>3</sup> -pseudocumene	( 7.24	0.12 )	x 10 <sup>-5</sup>	
	( 8.46	0.09 )	x 10 <sup>-5</sup>	
	( 8.08	0.04 )	x 10 <sup>-5</sup>	
	( 8.07	0.09 )	x 10 <sup>-5</sup>	
	( 6.73	0.13 )	x 10 <sup>-5</sup>	
	( 7.83	0.06 )	x 10 <sup>-5</sup>	
	( 8.77	0.22 )	x 10 <sup>-5</sup>	
	( 7.64	0.20 )	x 10 <sup>-5</sup>	
	( 7.08	0.19 )	x 10 <sup>-5</sup>	

TABLE 2 (continued)

<u>Compound</u>	<u>k</u>	<u><math>\sigma_k^a</math></u>	<u>(sec<sup>-1</sup>)</u>	<u><math>\frac{T^b}{(^{\circ}\text{C})}</math></u>
2-H <sup>3</sup> -mesitylene	( 7.22	0.14 )	x 10 <sup>-2</sup>	
	( 6.93	0.20 )	x 10 <sup>-2</sup>	
	( 6.88	0.13 )	x 10 <sup>-2</sup>	
	( 6.01	0.14 )	x 10 <sup>-2</sup>	
5-H <sup>3</sup> -prehnitene	( 1.17	0.11 )	x 10 <sup>-2</sup>	
	( 1.11	0.07 )	x 10 <sup>-2</sup>	
4-H <sup>3</sup> -isodurene	( 3.21	0.16 )	x 10 <sup>-3</sup>	13.1
	( 4.17	0.11 )	x 10 <sup>-3</sup>	16.2
	( 1.42	0.07 )	x 10 <sup>-2</sup>	30.0
	( 2.97	0.09 )	x 10 <sup>-2</sup>	40.0
3-H <sup>3</sup> -durene	( 7.51	0.36 )	x 10 <sup>-3</sup>	
	( 7.23	0.22 )	x 10 <sup>-3</sup>	
6-H <sup>3</sup> -pentamethyl- benzene	( 8.34	0.24 )	x 10 <sup>-3</sup>	9.8
	( 7.99	0.28 )	x 10 <sup>-3</sup>	9.8
	( 8.17	0.33 )	x 10 <sup>-3</sup>	9.8
	( 4.35	0.12 )	x 10 <sup>-2</sup>	30.0
	( 4.58	0.26 )	x 10 <sup>-2</sup>	30.0

(a) Standard error of the estimate of k as calculated by the least squares program OLS.

(b) Temperature of measurement. (70.0°C unless otherwise stated.)

TABLE 3

Rate-Constants for Detritiation at 70.0°C

<u>Compound</u>	<u>k</u>	<u><math>\sigma^a</math></u>	<u>lit.<sup>d</sup></u>	<u>(sec<sup>-1</sup>)</u>
H <sup>3</sup> -benzene	( 4.9	1.2	9.5 )	x 10 <sup>-9</sup>
o-H <sup>3</sup> -toluene	( 1.896	0.033	2.08 )	x 10 <sup>-6</sup>
m-H <sup>3</sup> -toluene	( 5.87	0.50	5.77 )	x 10 <sup>-8</sup>
p-H <sup>3</sup> -toluene	( 4.078	0.035	4.27 )	x 10 <sup>-6</sup>
3-H <sup>3</sup> -o-xylene	( 1.260	0.043	1.27 )	x 10 <sup>-5</sup>
4-H <sup>3</sup> -o-xylene	( 1.813	0.015	1.80 )	x 10 <sup>-5</sup>
2-H <sup>3</sup> -m-xylene	( 3.653	0.041	3.78 )	x 10 <sup>-4</sup>
4-H <sup>3</sup> -m-xylene	( 7.27	0.38	7.50 )	x 10 <sup>-4</sup>
5-H <sup>3</sup> -m-xylene	( 4.263	0.065		x 10 <sup>-7</sup>
2-H <sup>3</sup> -p-xylene	( 1.492	0.049	1.39 )	x 10 <sup>-5</sup>
4-H <sup>3</sup> -hemimellitene	( 2.396	0.028		x 10 <sup>-3</sup>
5-H <sup>3</sup> -hemimellitene	( 8.23	0.25		x 10 <sup>-5</sup>
3-H <sup>3</sup> -pseudocumene	( 1.560	0.021		x 10 <sup>-3</sup>
5-H <sup>3</sup> -pseudocumene	( 2.731	0.040		x 10 <sup>-3</sup>
6-H <sup>3</sup> -pseudocumene	( 7.77	0.22		x 10 <sup>-5</sup>
2-H <sup>3</sup> -mesitylene	( 6.76	0.26		x 10 <sup>-2</sup>
5-H <sup>3</sup> -prehnitene	( 1.14	0.05		x 10 <sup>-2</sup>
4-H <sup>3</sup> -isodurene	( 2.45 <sup>b</sup>	0.096 <sup>c</sup>		x 10 <sup>-1</sup>
3-H <sup>3</sup> -durene	( 7.37	0.14		x 10 <sup>-3</sup>
6-H <sup>3</sup> -pentamethyl- benzene	( 7.02 <sup>b</sup>	0.52 <sup>c</sup>		x 10 <sup>-1</sup>

- (a) Standard deviation of the estimate of the mean ( $\bar{k}$ ),  
 $= (s^2/n)$ , where  $s$  is the estimated standard  
deviation of the measurement,

$$s = \left( \sum_{i=1}^n (k - k_i)^2 / (n-1) \right)^{1/2}.$$

Hence the common formula:

$$\sigma_{\bar{x}} = \left( \sum_{i=1}^n (\bar{x} - x_i)^2 / (n(n-1)) \right)^{\frac{1}{2}} .$$

- (b) Calculated from Arrhenius Plot. (See page 67.)
- (c) See page 68.
- (d) See References 105, 106, 30, 81 and 107

TABLE 4

Arrhenius Plot Parameters for Detritiation at 70.0°C in Trifluoroacetic Acid<sup>a</sup>

Compound	$\Delta H^\ddagger$ (kcal/mole)	$\sigma_{\Delta H^\ddagger}$	$\sigma_{R.\ln(k)}^b$ (e.u.) <sup>c</sup>	$\Delta S^\ddagger$ (e.u.)	$\sigma_{\Delta S^\ddagger}$ (e.u.)	$\sigma_{RT.\ln(k)}^b$ (cal/mole)
3-H <sup>3</sup> -pseudocumene	16.78 16.76	0.21	0.071	-22.72 -22.72	0.65	23.0
5-H <sup>3</sup> -pseudocumene	16.32 16.31	0.17	0.063	-22.95 -22.98	0.56	22.0
4-H <sup>3</sup> -isodurene	14.24 14.24	0.17	0.042	-20.08 -20.10	0.58	13.0
6-H <sup>3</sup> -pentamethyl- benzene	13.61 13.61	0.27	0.073	-19.83 -19.83	0.90	21.0

(a) For each compound the first line is the result of a plot of  $R.\ln(kh)/kT$  against  $1/T$ ; the second line is the result of a plot of  $RT.\ln(kh)/kT$  against  $T$ . In each case a standard error is obtained for the slope of the least squares line, but not for the intercept. See also pages 83, 156.

(b)  $\sigma_{R.\ln(k)}$  and  $\sigma_{RT.\ln(k)}$  are the standard deviations of the points from the corresponding lines.

(c) Entropy units are cal.degree<sup>-1</sup>.mole<sup>-1</sup>.



(B) N.M.R. Proton Shifts of Polymethylbenzenes

The N.M.R. spectra of the polymethylbenzenes were recorded using both  $\text{CCl}_4$  and n-hexane as solvents. Solutions of aromatics (6%, v/v), containing tetramethylsilane as an internal reference, were studied using the Varian A60 spectrometer. Chemical shifts are tabulated below, together with literature values.

TABLE 5

Chemical Shifts Relative to T.M.S. for Ring Protons of the Polymethylbenzenes

<u>Position of</u> <u>Methyl Groups</u>	<u><math>\tau_{\text{CCl}_4}</math></u> (ppm)	<u>Literature</u>		<u><math>\tau_{\text{n-hex}}</math></u> (ppm)	<u>Solvent Shift</u> $\tau_{\text{CCl}_4} - \tau_{\text{n-hexane}}$
		(a)	(b)		
	2.73	2.73	2.78	2.78	-0.05
1 <sup>c</sup>	2.91	2.90	2.93	2.93	-0.02
1,2 <sup>c</sup>	3.03	2.99	3.03	3.03	0.0
1,3 <sup>c</sup>	3.13	3.11	3.12	3.11	0.02
1,4	3.05	3.05	3.06	3.07	-0.02
1,2,3 <sup>c</sup>	3.14	-	3.15	3.15	-0.01
1,2,4 <sup>c</sup>	3.18	-	3.17	3.17	0.01
1,3,5	3.33	3.36	3.33	3.32	0.01
1,2,3,4	3.26	-	-	3.23	0.03
1,2,3,5	3.33	-	-	3.30	0.03
1,2,4,5	3.25	3.26	-	3.23	0.02
1,2,3,4,5	3.34	3.32	-	3.30	0.04

(a) Reference 40, 2.5% in  $\text{CCl}_4$ .

(b) Reference 39, 2-3% in  $\text{CCl}_4$ .

(c) Value for largest peak.

TABLE 6

Chemical Shifts Relative to T.M.S. for Methyl Protons of  
the Polymethylbenzenes

<u>Position of Other</u> <u>Methyl Groups</u>	$\tau_{\text{CCl}_4}$ (ppm)	<u>Literature</u> (ppm) (a) (b)		$\tau_{\text{n-hexane}}$ (ppm)	<u>Solvent Shift</u> $\tau_{\text{CCl}_4} - \tau_{\text{n-hexane}}$
	7.67(5)	7.63	7.73	7.71(5)	-0.04
2	7.78	7.75	7.82	7.81	-0.03
3	7.72(5)	7.70	7.77	7.75	-0.02(5)
4	7.72(5)	7.71	7.78	7.76(5)	-0.04
2,3	7.76		7.82	7.79	-0.03
2,6	7.87		7.93	7.89	-0.02
2,4	7.82		7.86	7.84	-0.02
2,5	7.82		7.86	7.84	-0.02
3,4	7.77		7.81	7.79	-0.02
3,5	7.77(5)	7.75	7.81	7.79	-0.01(5)
2,3,4	7.79			7.81	-0.02
2,3,6	7.86			7.86(5)	-0.00(5)
2,3,5	7.81			7.81(5)	-0.00(5)
2,4,6	7.91(5)			7.92(5)	-0.01
3,4,5	7.81			7.81(5)	-0.00(5)
2,4,5	7.86	7.85		7.87(5)	-0.01(5)
2,3,4,5	7.82(5)	7.82		7.84	-0.01(5)
2,3,4,6	7.87(5)	7.87		7.87	-0.00(5)
2,3,5,6	7.82(5)	7.82		7.84	-0.01(5)
2,3,4,5,6	7.83	7.83		7.85	-0.02

(a) Reference 41

(b) Reference 39

(C) Discussion of Measurements

(i) Rates of Detritiation

(1) H<sup>3</sup>-benzene

This value represents a half life of about four and a half years, and is substantially smaller than the value obtained by Baker and Eaborn.<sup>66</sup> Two runs were conducted over a period of a year, but in both the first three points showed increasing count-rates when the runs were eventually counted. This was at first attributed to loss of benzene from the toluene scintillator solution during the prolonged storage, as no excessive quenching of these solutions could be detected. However, two more runs, over a period of two months, with a new batch of both hydrocarbon and acid showed much the same behaviour. The large difference between the rate-constants obtained from the remaining eight months of the first two runs (even when the large errors of the estimates are considered), appear to indicate an exceptional sensitivity to impurities, perhaps not surprising in view of the extreme slowness of reaction. As investigations of catalysts in this medium<sup>67</sup> have not yet shown any that slow the reaction when present in trace quantities, it would appear likely that the larger values are in error. No discussion of errors and experimental difficulties is available from earlier work.

The value adopted is the average of the rate-constants obtained from the first two runs, neglecting the first three points of each.

(2) m-H<sup>3</sup>-toluene

To a lesser extent the problems of measuring slow reactions were also encountered for m-H<sup>3</sup>-toluene. However, here the reaction was observed for over one half-life with a consequent improvement in accuracy. Low activities of early samples were not observed for m-H<sup>3</sup>-toluene. Once again the large variation between runs is reflected in a large estimated standard error.

(3) 6-H<sup>3</sup>-pseudocumene

Nine runs were conducted for 6-H<sup>3</sup>-pseudocumene as considerable variation was observed in the first few results. The resulting mean should be a reliable value.

(4) 5-H<sup>3</sup>-prehnitene

Low activity of the tritiated hydrocarbon made measurement of this rate-constant difficult. The estimate of this error may be too low.

(5) 6-H<sup>3</sup>-pentamethylbenzene

This error may be over-estimated. Although the Arrhenius plot was necessarily conducted over a narrow temperature range, the parameters compare well with those of other compounds. (Table 4) See also page 85.

(ii) Nuclear Magnetic Resonance Spectra

It is estimated that the error of each peak measurement is less than 0.01 ppm for all peaks except for the smallest methyl peak of pentamethylbenzene which is rather broader than the others. The measurements are therefore expected to show a standard deviation of about 0.005 ppm due to experimental error.

The assignments of the methyl peaks are discussed later (page 144).

## DISCUSSION OF RESULTS

### (A) Detritiation Results

#### (i) Arrhenius Parameters

##### (1) Determination of the Arrhenius Parameters

The measurement of the temperature dependence of the rate-constants for detritiation of four of the polymethylbenzenes was described earlier (page 67). The activation enthalpies ( $\Delta H^\ddagger$ ) and entropies ( $\Delta S^\ddagger$ ) were derived and are shown in Table 4. Their values rely on the usual assumption that the heat capacity of activation is zero.

$$\Delta C_p = (\partial \Delta H^\ddagger / \partial T) = T(\partial \Delta S^\ddagger / \partial T) = 0$$

Temperature dependence of  $\Delta C_p$  has been demonstrated for several reactions, but is thought likely to be small for proton transfer processes.<sup>68</sup> If this is true the free energy of activation can be expressed in terms of two temperature invariant functions

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

so that these can be obtained directly from the temperature dependence of the rate-constants using the absolute theory relationship<sup>17</sup>

$$\log_e k = \log_e (kT/h) - \Delta G^\ddagger/RT$$

where partition functions, quantum-mechanical tunnelling and transmission factors have been ignored.<sup>69,70</sup> The symbols

have been defined earlier (page 67 ). The equation for the error of the estimate of  $\Delta G^\ddagger$  at an extrapolated temperature was also given (page 69 ), but for the purposes of the next section a more detailed examination of the dependence of the error of  $\Delta H^\ddagger$  on the error of  $\Delta S^\ddagger$  is required.

If data of the form  $(x_i, y_i)$  where  $x, y$  are dependent variables and  $1, \dots, i, \dots, n$  are observations are used to obtain parameter estimates  $a$  and  $b$  by the method of least squares for the relation

$$y = a + bx$$

then

$$a = \bar{y} - b\bar{x}$$

where  $(\bar{x}, \bar{y})$  is the centroid of the data set.

$$\text{and } b = \left[ \sum_{i=1}^n (x_i - \bar{x})(y_i - \bar{y}) \right] / \left[ \sum_{i=1}^n (x_i - \bar{x})^2 \right]$$

Also the variances of these estimates are

$$V(a) = \left[ \sigma^2 \cdot \sum_{i=1}^n x_i^2 \right] / \left[ (n \sum_{i=1}^n (x_i - \bar{x})^2) \right] = \sigma_a^2$$

$$V(b) = \sigma^2 / \sum_{i=1}^n (x_i - \bar{x})^2 = \sigma_b^2$$

$$\text{where } \sigma^2 = \sum_{i=1}^n (y_i - a - bx_i)^2 / n$$

Now the "covariance" of  $a$  and  $b$  is defined as the average value of the function  $(a - a^t)(b - b^t)$  where  $a^t$  and  $b^t$  are the "true" values of the estimated quantities  $a$  and  $b$ .<sup>60</sup>

$$\begin{aligned} \text{Cov}(ab) &= \sigma^2 \bar{x} / \left[ \sum_{i=1}^n (x_i - \bar{x})^2 \right] \\ &= \bar{x} \cdot V(b) \end{aligned}$$

$$\left[ = \sigma_a \cdot \sigma_b \cdot \rho_{ab} \right] \quad \text{where } \rho_{ab} \leq 1 \text{ is the}$$

"correlation coefficient" usually supplied as an element of a "correlation matrix" in least squares computer program outputs.]

## (2) Isokinetic Relationship

For substituted molecules undergoing a given reaction it has been shown theoretically that the assumption  $\Delta C_p^\ddagger = 0$  leads to a linear relationship between  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for substituents with only a single mechanism of interaction.<sup>69</sup> Many examples of this behaviour have been observed,<sup>71</sup> but caution in interpreting the results is necessary. As was shown in the preceding section " $a = \bar{y} - b\bar{x}$ " is a fundamental least squares condition. Therefore, any error in "b" will appear in the estimate of "a" multiplied by the factor  $(-\bar{x})$ . (This relation is also suggested by the formula for the covariance of a and b.) Application of this result to a plot of  $\Delta H^\ddagger$  against  $\Delta S^\ddagger$  shows that a series of determinations having the same random errors will result in a straight line:-

$$\Delta H^\ddagger = \bar{T} \Delta S^\ddagger + \text{constant}$$

Random experimental errors can therefore account for "isokinetic" lines with slope close to the average experimental temperature ( $\bar{T}$ ) for a series with a small spread of reactivities and a range of parameter values which is small compared with their estimated errors.<sup>72</sup>

The plot of  $\Delta H^\ddagger$  v.  $\Delta S^\ddagger$  for detritiation is shown on page 85.



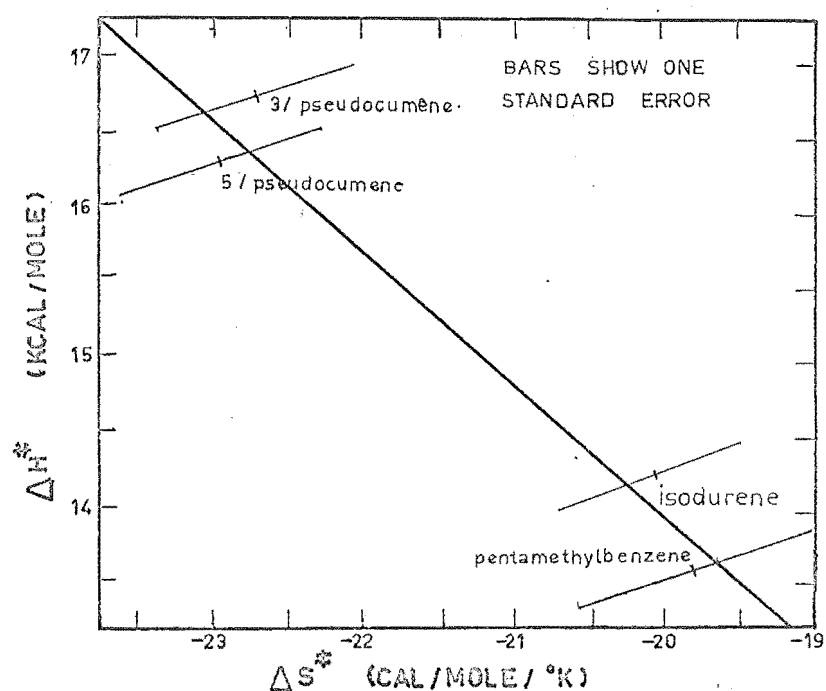
The regression line

$$\Delta H^{\ddagger} = \beta_1 \Delta S^{\ddagger} + \beta_2^{\ddagger}$$

gave the estimates  $\beta_1 = -904$ , s.e. = 3 ( $^{\circ}\text{K}$ );  $\beta_2 = -4.115$ , s.e. = 0.66 (kcal/mole). The multiple correlation coefficient was 0.981.

The coefficient  $\beta_1$  has been called the isokinetic temperature since the relationship implies that  $T = \beta_1$  makes  $\Delta G^{\ddagger} = \beta_2$  for all the compounds of the series, which therefore have the same rate-constant. The observed large negative value of  $\beta_1$  is very unusual. In an early tabulation by Leffler<sup>73</sup> values ranging from  $+70$  -  $+1320^{\circ}\text{K}$  were obtained for 79 reaction series. The positive values were rationalised

FIGURE 10.



ISOKINETIC RELATIONSHIP IN DETRITIATION

by arguing that substituents which decrease the activation enthalpy require a more restricted solvent geometry, and so give a more negative activation entropy.<sup>69</sup>

Whereas the spread of activation enthalpies for the four polymethylbenzene positions measured is 3.2 kcals/mole, the spread of activation entropies represents a range of 1.1 kcals/mole of free energy. In spite of the substantial errors in the entropy values it is clear that a major part of the substituent effect is due to a change in the enthalpy term despite earlier work on dedeuteration in  $\text{CF}_3\text{COOH}/\text{H}_2\text{SO}_4$  mixtures by Mackor, Smit, and van der Waals<sup>32</sup> which indicated that the entropy term might predominate. Their results do support the more positive entropy of activation for more reactive polymethylbenzenes.

It is apparent that the entropy term arises from a combination of at least two interactions. The incipient trifluoroacetate anion and the Wheland intermediate cation must both be solvated. The degree of proton transfer in the transition state will be the determining factor for the first entropy difference. According to both the Hammond postulate<sup>13</sup> and recent work on reaction trajectories on potential energy surfaces,<sup>74</sup> the higher the barrier the greater will be the extension of the breaking bond at the transition state. The more reactive polymethylbenzenes will therefore involve a smaller trifluoroacetate solvation entropy.

If the substituent effect is considered to arise from "charge spreading", then the methyl groups must bear a greater amount of the charge of the Wheland intermediate than hydrogen atoms. On the other hand, as substitution increases the reactivity of the system, there will be less charge in the transition state to be solvated. A further possibility is the loss of methyl rotational freedom because of hyperconjugation.

The interplay of these effects affords the possibility of a variety of resultants, and it is perhaps not surprising that the Baker-Nathan order of substituent effects ( $\text{CH}_3$ - more electron releasing than  $t\text{-Bu-}$ ) is apt to reverse on change of solvents.<sup>28</sup>

### (3) Comparison of Values of the Arrhenius Parameters

The standard state of the free energy of activation is defined by the scale used to express the rate-constant  $k$  in the equation:-

$$\log_e k = \log_e (\underline{kT/h}) - \Delta G^\ddagger / RT$$

( $\underline{kT/h}$  is expressed in units of  $(\text{time})^{-1}$ )<sup>70</sup>

The units of  $k$  used for this work were  $\text{sec}^{-1}$ , but the implication of a concentration term owing to the pseudo first-order nature of the kinetics must be remembered if comparisons are to be made with other systems. This correction factor, which is also necessary for comparison with unimolecular or termolecular reactions, will appear in the entropy term if it is largely independent of

temperature.

Differences in free energy, enthalpy or entropy between measurements involving the same standard state are independent of the standard state, and may be compared directly.

The free energies of activation obtained spanned the range 20.4 - 33.2 kcals/mole, and represented very similar reactivities to those observed for deuteration and bromination of the polymethylbenzenes.

The large negative values for the entropies of activation are common for reactions involving Wheland intermediates, and have been ascribed to solvation effects.<sup>75</sup>

(ii) The Additivity Principle

(1) Previous Work

Since it was first proposed by Condon<sup>24</sup> the Additivity Principle has been tested for many electrophilic substitution reactions using the polymethylbenzene series. The alkyl groups have been the favoured substituents; they have relatively small  $\sigma$  values so that rates for a wide range of polysubstituted benzenes can be measured in spite of the very large  $\rho$  values encountered in aromatic substitutions. (e.g. Bromination,  $\rho = 12.1$ ;<sup>76</sup> Chlorination,  $\rho = 10.0$ ;<sup>77</sup> Detritiation,  $\rho \sim 10$ <sup>78</sup> depending on solvent.)

This marked selectivity is sensitive to the solvent, and this has presented difficulties when measurements made in different solvents have been compared. Because of the necessity to use more reactive, less selective reagent solutions for the less reactive substituted aromatics, the reported agreement with the Additivity Principle for some of the early work may appear rather better than is really the case.

For a large number of reactions it has been shown that the polymethylbenzenes react much more slowly than predicted by the Additivity Principle.<sup>25</sup> In many cases it can be seen that steric factors are not causing the deviations, because a smooth trend is observed with increasing reactivity and durene, with its severely hindered reaction

site, always appears quite close to the Additivity prediction. In particular, Baciocchi and Illuminati<sup>25</sup> have shown that for several series of substituted tetramethylbenzenes and substituted mesitylenes, cylindrically symmetrical substituents (e.g. -CN, -Me, -Cl) result in predictable effects on the reactivity of the remaining unsubstituted position towards electrophilic attack (e.g. bromination and chlorination). They obtain good correlations with values obtained from substituted benzenes, but  $\rho$  values are decreased by 25% in spite of less reactive, and hence more selective, solvent systems being employed.

It should be noted that deviations from additivity are often no more than a factor of 2-4 in spite of reactivity ranges of the order of  $10^8$ , so that from a practical point of view the Principle is quite as successful as most Hammett correlations. Nevertheless, the fact that only one type of substituent need be used eliminates variations in substituent-solvent interactions, and as deviations from additivity do not appear to be random, there appears to be a good chance of improving the theory.

## (2) Experimental Difficulties

Where hydrogen is the substituent displaced in the course of the reaction, the problem of detecting the relative amounts of substitution in the various positions of the unsymmetrical polymethylbenzenes may be severe, especially for the less reactive positions which account for only a fractional percentage of the total reaction products. (For instance the 5-position of m-xylene.) In these reactions much work measured only the relative substrate selectivities, that is the relative overall reactivities of the hydrocarbons. One value would then be known for each molecule, and would be assumed to be the sum of the reactivities at all the possible ring positions. These would then be compared (using the Additivity Principle) with product distributions obtained for toluene (in which the meta value was often subject to considerable error).

A more severe test was made possible by the development, largely by Eaborn and his co-workers, of displacement reactions where the position of substitution could be predetermined, and thus difficult product analyses avoided. Reactions such as proto-degermylation and -desilylation showed steric acceleration when the reaction site was either "flanked" by two ortho methyl groups or "buttressed" by an ortho and meta combination on the same side of the ring.<sup>19</sup> This complication could be avoided

by using the other hydrogen isotopes and the extension of Eaborn's detritiation measurements to cover the whole series of the polymethylbenzenes has been completed by the present work.

The problem of correcting for different solvents has been avoided by modifying the experimental techniques so that a range of reactivities of over  $10^7$  could be measured at the same temperature in the same reagent medium. This was achieved at some cost to accuracy at the extremes of the range, but it is considered that the errors are likely to be smaller than those arising from changing conditions. (For example, the detritiation reactivity of the ortho position of toluene relative to the para position, has been shown to vary from 1.1 to 0.3 as the exchanging acid becomes more selective.)<sup>79</sup> By means of temperature dependence measurements of rate-constants, the range was extended by another power of 10. Furthermore, individual measurements of temperature dependence were made in the two cases where extrapolation was required, and these extrapolations were compared with others for which measurements were also made at 70°C. This represents a more complete study than the earlier deuteration work<sup>31</sup> in which comparisons made at lower temperatures were assumed to be valid for higher temperatures.

Modern "general least squares" (non-linear) computer



programs make possible the direct determination of rate-constants from the exponential decay curves and allow easy correction for a finite end-point concentration, so that curvature of log plots for fast reactions is no longer a problem.

### (3) Detritiation and the Additivity Principle

The results of Eaborn and his co-workers for detritiation in trifluoroacetic acid at 70.0°C have established values for the partial rate factors of 220, 6.1, 450, for ortho, meta, and para methyl groups respectively.<sup>80,81</sup> Even with these values applied to the xylenes marked discrepancies had been found, with the 2 and 4 positions of m-xylene being about 20% less reactive than predicted, and the 4 position of o-xylene being about 30% too low.<sup>30</sup>

Agreement may actually be considerably worse than this as the results of the present work suggest that the accepted value for benzene may be too high by up to a factor of two.

The results of a regression analysis assuming additivity for the detritiation results obtained in this work are shown in Table 7 and Figure 11. The results show a distinct curvature with deviations that appear to be independent of the steric environment of the reaction site.

The partial rate factors obtained are much smaller than those measured for toluene and clearly represent a compromise between large effects for the unreactive compounds,

and small effects for the very reactive polymethylbenzenes.  
(See also Figure 15.)

TABLE 7

Least Squares Analysis of Additivity for Detritiation<sup>a</sup>

	<u><math>\beta</math></u>	<u>Standard Error</u>	<u>Factors<sup>b</sup></u>	<u>Literature<sup>c</sup></u>
log o	2.172	0.022	149	220
log m	0.730	0.021	5.4	6.1
log p	2.359	0.032	229	450
Intercept -7.846				
Standard Error of Estimate <sup>d</sup>			0.135 (37%)	
Multiple Correlation Coefficient			0.997	

(a) Using STEPR (page 52). The relation assumed was  $\log k = \beta_1 + n_o \beta_2 + n_m \beta_3 + n_p \beta_4$  where the  $\beta$ 's are regression coefficients;  $n_o$ ,  $n_m$ , and  $n_p$  are the numbers of methyl groups ortho, meta, and para respectively to the reaction site.

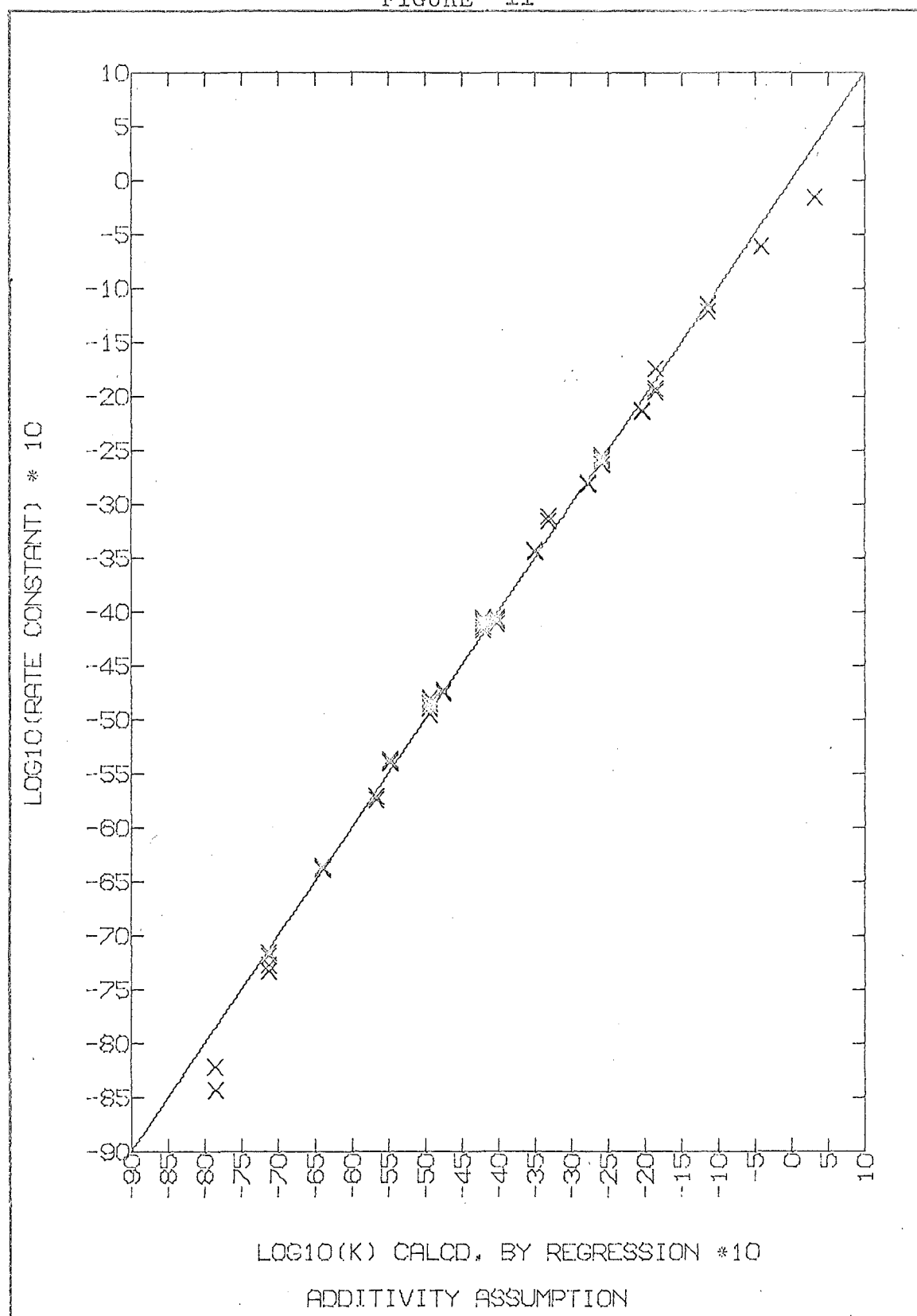
(b) Partial rate factors corresponding to the  $\beta$  values.

(c) Partial rate factors for toluene according to Eaborn and his co-workers.<sup>80,81</sup>

(d) This analysis was carried out using the whole set of "unaveraged" rate-constants and so was weighted according to experimental error. For a comparison of these results with the "averaged" rate-constants see Table 9.

Note, that standard error is larger than this.

FIGURE 11

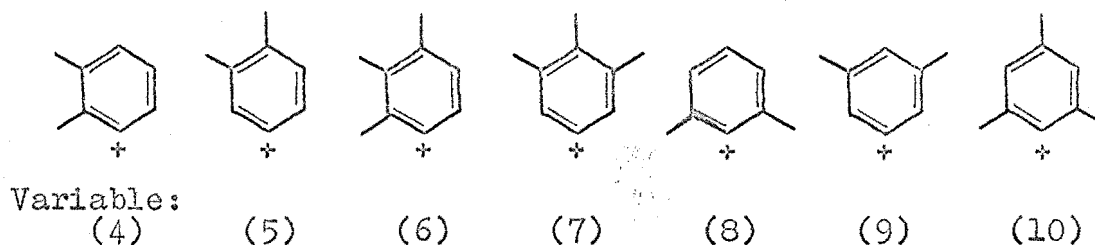


The regression analysis was continued making allowance for second order interactions.  $n_b$  represented the number of "buttressed" ortho-meta combinations (i.e. both substituents on the same side of the ring.) Other interaction variables were included in the analysis as shown below.

<u>No.</u>	<u>Variable<sup>a</sup></u>	<u>Name/Explanation<sup>b</sup></u>
1	$n_o$	Ortho
2	$n_m$	Meta
3	$n_p$	Para
4	$n_b$	Ortho/Meta Buttressed
5	$n_m \cdot n_p$	Meta/Para Buttressed
6	$n_b \cdot n_p$	Flanked Metas
7	$(n_m \cdot n_p - 1) \cdot n_m \cdot n_p / 2$	Flanked Paras
8	$(n_o - 1) \cdot n_o / 2$	Double Orthos
9	$(n_m - 1) \cdot n_m / 2$	Double Metas
10	$n_o \cdot n_p$	Ortho/Para Interaction

(a) The functions shown here are merely designed to calculate the number of times the structural feature named in the third column appears in a given transition state using the values  $n_o$ ,  $n_m$ ,  $n_p$ , and  $n_b$  which were provided as computer input for each observed rate-constant.

(b) Examples in which variables 4-10 take the value 1 are shown below. The reaction site is marked "+". Methyl groups are shown by lines.

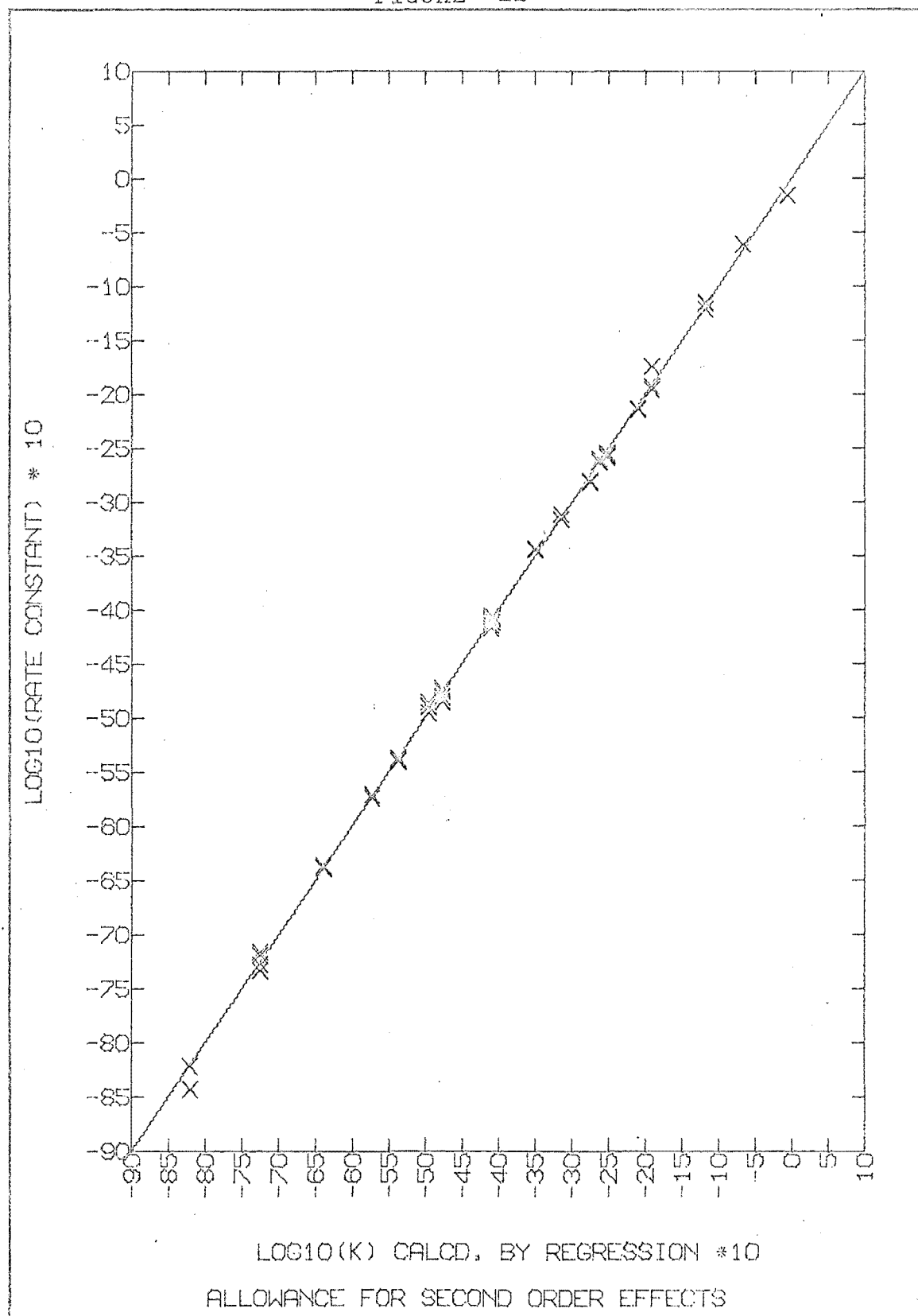


As explained previously (page 66) selection of the most significant variables first was automatic. The correlation shown in Figure 12 and Table 8 was obtained. It is evident that no simple explanation for the non-additive behaviour is provided although interesting features are brought to light:-

- (a) The most important second order correlation is the buttressing of a para substituent (5) which reduces its effect by over a half.
- (b) Buttressing of ortho groups (4), and the hindered position between two substituents ("double orthos") (8) both result in reduced reactivity, but the similar effect for ortho-para interaction (10) must urge caution in considering these as simple steric effects on the reaction site.
- (c) The increased reactivity for the flanked positions (6,7) should be interpreted as a reduced effect for the

FIGURE 12

98



second buttressing. Particularly for the flanked meta (6), this is rather surprising.

TABLE 8

Analysis of Additivity Including Second Order Interaction Terms

<u>Variable</u> <u>Number</u> <sup>a</sup>	<u>Regression</u> <u>Coefficient</u>	<u>Standard</u> <u>Error</u>	<u>Factor</u> <sup>b</sup>	<u>Order</u> <u>Chosen</u>
1	+2.498	0.025	315.00	1
2	+0.958	0.030	9.10	3
3	+2.837	0.037	687.00	2
4	-0.203	0.027	0.63	7
5	-0.348	0.040	0.45	4
6	+0.113	0.038	1.30	8
7	+0.186	0.058	1.54	9
8	-0.286	0.031	0.52	6
9	-0.101	0.040	0.79	10
10	-0.257	0.026	0.55	5
Intercept	-8.218			
Standard Error of Estimate		0.063		
Multiple Correlation Coefficient		0.9995		

(a) See page 96.

(b) Antilog of Regression Coefficient.

TABLE 9

Least Squares Correlations for Detritiation  $-\log_{10} k$  Values

Compound	Obs <sup>a</sup>	Calc <sup>b</sup>	Obs-Calc	Calc <sup>c</sup>	Obs-Calc
H <sup>3</sup> -benzene	8.32	7.85	-0.47	8.22	-0.10
o-H <sup>3</sup> -toluene	5.72	5.67	-0.05	5.72	0.00
m-H <sup>3</sup> -toluene	7.24	7.12	-0.12	7.26	+0.02
p-H <sup>3</sup> -toluene	5.39	5.49	+0.10	5.38	-0.01
3-H <sup>3</sup> -o-xylene	4.89	4.94	+0.05	4.97	+0.08
4-H <sup>3</sup> -o-xylene	4.74	4.76	+0.02	4.77	+0.03
2-H <sup>3</sup> -m-xylene	3.44	3.50	+0.06	3.51	+0.07
4-H <sup>3</sup> -m-xylene	3.14	3.32	+0.18	3.14	0.00
5-H <sup>3</sup> -m-xylene	6.38	6.39	+0.01	6.40	+0.02
2-H <sup>3</sup> -p-xylene	4.83	4.94	+0.11	4.76	-0.07
4-H <sup>3</sup> -hemimellitene	2.62	2.59	-0.03	2.62	0.00
5-H <sup>3</sup> -hemimellitene	4.09	4.03	-0.06	4.07	-0.02
3-H <sup>3</sup> -pseudocumene	2.81	2.77	-0.04	2.75	-0.06
5-H <sup>3</sup> -pseudocumene	2.56	2.59	+0.03	2.53	-0.03
6-H <sup>3</sup> -pseudocumene	4.11	4.21	+0.10	4.11	0.00
2-H <sup>3</sup> -mesitylene	1.17	1.14	-0.03	1.19	+0.02
5-H <sup>3</sup> -prehnitene	1.94	1.86	-0.08	1.92	-0.02
4-H <sup>3</sup> -isodurene	0.61	0.41	-0.20	0.66	+0.05
3-H <sup>3</sup> -durene	2.13	2.04	-0.07	2.10	+0.03
6-H <sup>3</sup> -pentamethyl- benzene	0.15	-0.32	-0.47	0.06	-0.09
Standard Error of Estimates			0.17		0.048

(a) Calculated from the results listed in Table 3.

(b) See page 94. (Additivity approximation.)

(c) See page 96. (Allowance for interaction terms.)



(4) Detritiation as a Model Reaction for Electrophilic  
Substitution

Because of its low steric requirements, symmetrical Wheland intermediate and high selectivity, hydrogen exchange has a strong claim to be considered a good model of basic electronic effects in electrophilic substitution, and to this end comparisons with some of the better additivity plots are shown in Figures 13 and 14. (The relative overall reactivities used for detritiation are calculated from the positional reactivities and shown in Table 10, together with some from other reactions.)

With the exception of acetylation, whose steric requirements are evidently very severe, the correlations yield good straight lines with the major deviations consistently appearing for p-xylene and durene in a manner that suggests they are related to the steric requirements of the electrophile. (For example, deviations for p-xylene increase in the order  $D \sim Cl < Br \sim Hg < CO < Ac.$ )

Partial rate factors for various electrophilic substitution reactions of toluene are shown in Table 11, and show a great variety of ortho/para ratios which make the correlations with the detritiation results most surprising at first sight. The sensitivities of the various overall rate-constants of the polymethylbenzenes towards changes in the ortho partial rate factor were therefore investigated theoretically assuming the Additivity

FIGURE 13

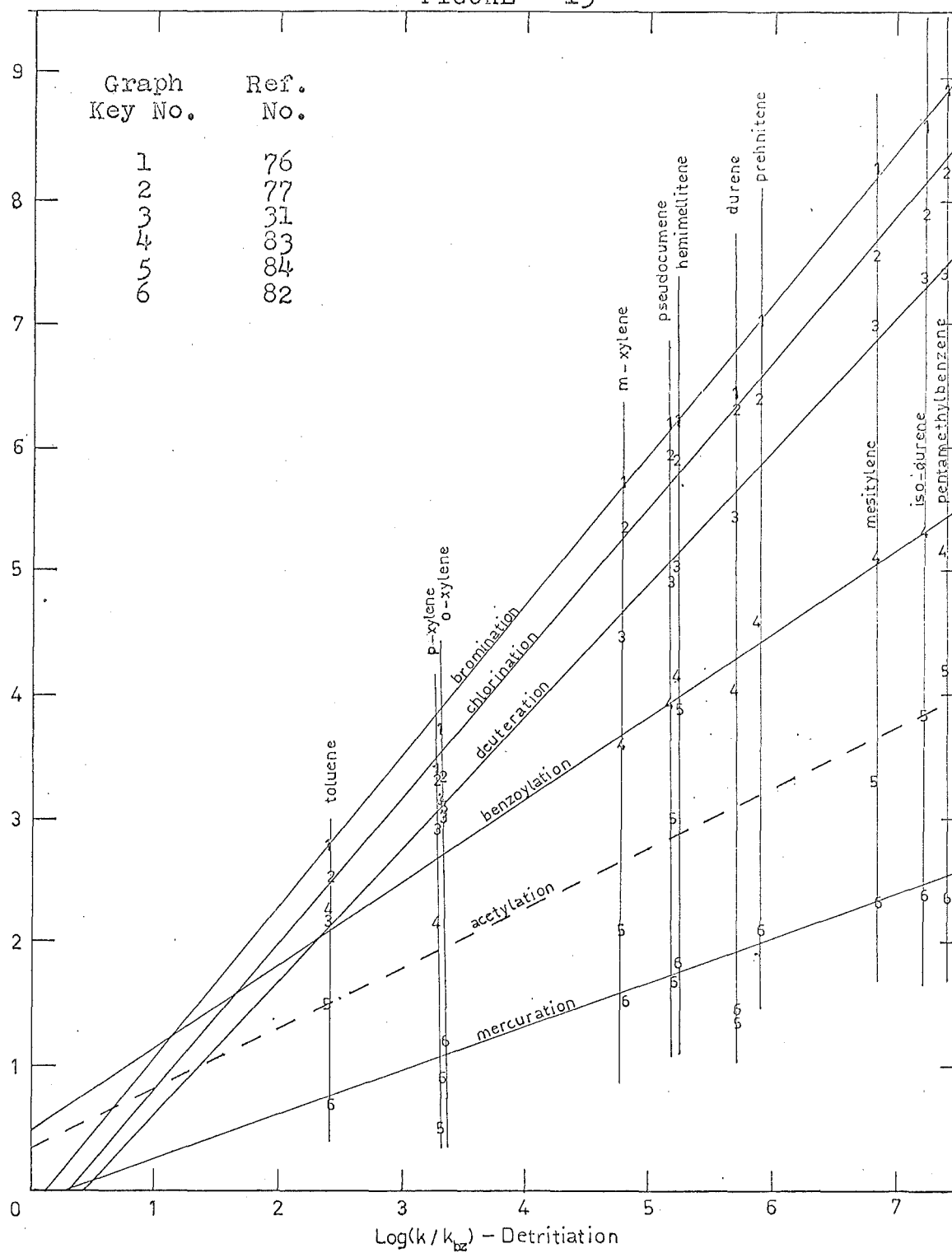


TABLE 10

Comparison of Relative Rates for Electrophilic Substitutions  
in the Polymethylbenzenes

<u>Compound</u>	<u>Detritiation</u>	<u>Deuteration</u>	<u>Bromination</u>	<u>Mercuration</u>
	$\log k_{\text{rel}}^{\text{a}}$	$\log k_{\text{rel}}^{\text{b}}$	$\log k_{\text{rel}}^{\text{c}}$	$\log k_{\text{rel}}^{\text{d}}$
Benzene	0.0	0.0	0.0	0.0
Toluene	2.43	2.19	2.78	0.70
o-Xylene	3.32	3.01	3.73	1.21
m-Xylene	4.79	4.48	5.71	1.54
p-Xylene	3.31	2.93	3.40	0.92
Hemimellitene	5.22	5.04	6.22	1.84
Pseudocumene	5.17	4.92	6.18	1.70
Mesitylene	6.84	6.98	8.28	2.33
Prehnitene	5.89	-	7.04	2.11
Isodurene	7.23	7.40	8.62	2.41
Durene	5.70	5.45	6.45	1.48
Pentamethyl- benzene	7.38	7.42	8.91	2.36

(a) Calculated from the results listed in Table 3 assuming additivity of positional reactivities and taking benzene as unit reactivity.

(b) Reference 31.

(c) Reference 76.

(d) Reference 82.

TABLE 11<sup>a</sup>

Partial Rate Factors for Electrophilic Substitution Reactions  
of Toluene

<u>Reaction</u>	<u>Conditions</u>	<u><math>\sigma_f</math></u>	<u><math>m_f</math></u>	<u><math>\rho_f</math></u>
Bromination	$\text{Br}_2/\text{HAc}/\text{H}_2\text{O}/25^\circ$	600	5.5	2420
Chlorination	$\text{Cl}_2/\text{HAc}/25^\circ$	617	4.95	820
Deuteration	$\text{D}_2\text{O}/\text{CF}_3\text{COOH}/70^\circ$	253	3.8	420
Acetylation	$\text{AcCl}/\text{AlCl}_3/\text{C}_2\text{H}_4\text{Cl}_2/25^\circ$	4.5	4.8	749
Benzoylation	$\text{PhCOCl}/\text{AlCl}_3/\text{PhNO}_2/25^\circ$	32.6	5.0	831
Mercuration	$\text{Hg}(\text{OAc})_2/\text{HAc}/50^\circ$	4.60	1.98	16.8
Sulphonation	$14.8\text{M H}_2\text{SO}_4/25^\circ$	63.4	5.7	258
t-Butylation	$\text{tBuBr}/\text{SnCl}_4/\text{MeNO}_2/25^\circ$	0.0	3.2	93.2
t-Butylation	isobutylene/ $\text{AlCl}_3/\text{MeNO}_2$ @ $25^\circ$	0.0	3.55	84.1
Desilylation	$\text{HClO}_4/\text{MeOH}/\text{H}_2\text{O}/50^\circ$	18.3	2.4	22.8
Degermylation	$\text{HClO}_4/\text{MeOH}/\text{H}_2\text{O}/50^\circ$	12.4	2.11	14.0

(a) References to the work summarized in this table can be found in Reference 25 from which this table was taken.

Principle to be valid. If the partial rate factors for the ortho, meta, and para positions are designated  $\underline{o}$ ,  $\underline{m}$ , and  $\underline{p}$ , respectively, and  $k$  represents rates relative to benzene then it can be shown that the following overall dependences on the ortho partial rate factor are obtained. (See Table 12.)

It can be seen that Table 12 provides a good explanation of Figure 13. The correlations are the result of considerable linearity between  $\log k_{\text{detr.}}$  and the dependence on  $\underline{o}$ , as evidenced by the ratios  $R^{\text{Max}}/\log k_{\text{detr.}}$ . While a change of  $\underline{o}$  alters the slope of the correlating line in Figure 13, the resulting scatter is not severe.

o-Xylene, hemimellitene and prehnitene are particularly insensitive to  $\underline{o}$ , and for the first two this is accentuated as  $\underline{o}$  becomes smaller. p-Xylene, durene, and the three most reactive compounds should show greater sensitivity to  $\underline{o}$ . All these trends are clearly shown in the correlations of Figure 13. (For mesitylene, isodurene and pentamethylbenzene the deviations do not seem to be as marked as those predicted.)

Figure 14 shows correlations of the detritiation results with the basicities of the hydrocarbons towards HF measured in three different ways. Two of these have large errors for the more unreactive compounds (for the dotted line no value for benzene was available), but quite good straight lines are obtained indicating that the conjugate acid in HF is a good representation of the transition state

TABLE 12

Sensitivity of Rate-Constants to Changes in the Ortho Partial

Compound (Reactivity Order)	Rate Factor		$\log k_{\text{detrit.}}$	$R^{\text{Max}}/\log k_{\text{detrit.}}$
	$d(\ln k)/d(\ln o)^b$	$(= R)$		
Benzene	0.0		0.0	-
Toluene	0.0	$R^a < 0.5$	2.43	0.21
p-Xylene	1.0		3.31	0.30
o-Xylene	0.0	$R^a < 0.5$	3.32	0.15
m-Xylene	1.0	$R^a < 1.2$	4.79	0.25
Pseudocumene	1.0	$R^a < 1.3$	5.17	0.25
Hemimellitene	0.2	$R^a < 1.0$	5.22	0.19
Durene	2.0		5.70	0.35
Prehnitene	1.0		5.89	0.17
Mesitylene	2.0		6.84	0.29
Isodurene	2.0		7.23	0.28
Pentamethylbenzene	2.0		7.38	0.27

(a) Upper limits were calculated assuming  $o/p = 0.5$  as observed for detritiation. Lower limits are the asymptotes approached as  $o/p \rightarrow 0.0$

(b)  $k$  is the overall reactivity relative to the total reactivity of the six positions of benzene.

$$\text{e.g. for toluene } k = (2o + 2m + p)/6$$

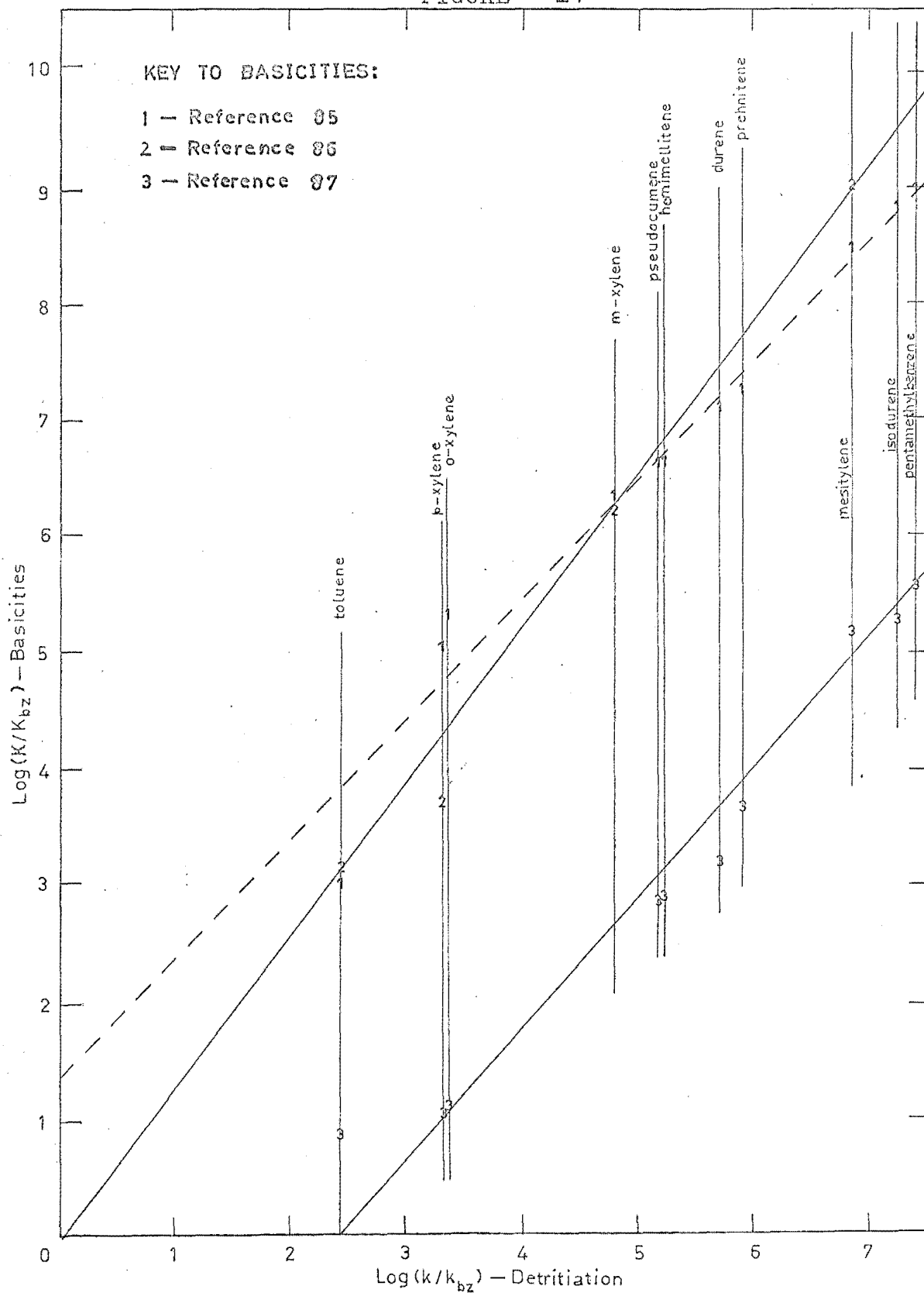
$$\therefore d(\ln k) = 2do/(2o + 2m + p)$$

$$= 2/(2 + (2m + p)/o) \cdot d(\ln o)$$

For detritiation  $(2m + p)/o \sim 2$ .

$\therefore$  Maximum value of  $R = 0.5$ , and  $R \rightarrow 0$  as  $o \rightarrow 0$ .

FIGURE 14



RELATIVE BASICITIES OF THE POLYMETHYLBENZENES

in the detritiation reaction. The fact that the slopes are not substantially different from unity indicate that either electron demand is very similar to that in the transition state of detritiation in trifluoroacetic acid, or that the methyl substituents are not as effective in HF solutions as they are in weaker acids.



(iii) Saturation of Substituent Effects(1) Nature of the Methyl Group

As a substituent, the methyl group is notable for its comparatively small perturbation of the benzene ring. The dipole moment of toluene is less than 25% of that of many other monosubstituted benzenes. (Table 13.<sup>88</sup>)

TABLE 13

Dipole Moments of Monosubstituted Benzenes<sup>88</sup>

<u>Compound</u>	<u><math>\mu \times 10^{18}</math> esu</u>
Toluene	0.36 $\pm$ 0.03
Anisole	1.38 -
Chlorobenzene	1.70 $\pm$ 0.04
Fluorobenzene	1.58 $\pm$ 0.02
Phenol	1.45
Aniline	1.53

The electronegativities of a hydrogen atom and a methyl group have been calculated in a number of ways (Table 14) and appear to be very similar.<sup>89</sup>

The very great stabilization of the transition state shown by the methyl group as a substituent in the detritiation of methylbenzenes, and other electrophilic substitutions, must then be attributed to its polarisability, rather than a static effect such as a permanent dipole. The amount of stabilization, or of electron donation in this case, should vary with the demand. As greater

positive charge is developed in the activated complex, the difference between a hydrogen atom and a methyl group as a source of electrons will become more apparent, and this is the basis of Brown's Selectivity Relationship.

TABLE 14

Group Electronegativities<sup>89</sup>

<u>-R</u>	<u>X<sub>R</sub><sup>a</sup></u>	<u>X<sub>R</sub><sup>b</sup></u>	<u>X<sub>R</sub><sup>c</sup></u>
-H	2.28	2.17	2.28
-Me	2.30	2.62	2.30
-Cl	3.30	3.00	3.00

(a) Mutually consistent empirical values.

(b), (c) Calculated by two different methods.

The substituent effects for addition of a methyl group, either ortho, meta, or para, to the site of detritiation are shown on page 111 for all the polymethylbenzenes. It can be seen that as log k becomes larger (less negative),  $\Delta \log k$  becomes smaller for all three positions of substitution. [log k refers to a compound with n methyl groups. ( $\Delta \log k + \log k$ ) refers to one with n+1 methyl groups.] This effect is a decrease in the partial rate factors as the reactivity of the aromatic increases. Such a dependence on increased reactivity is usually interpreted as a change in the structure of the activated complex so as to make it less like that of the Wheland intermediate, and require less charge stabilization from the substituents.

Observed Substituent Increments ( $\Delta \log k$ ) and Log  $k$  Values  
for Detritiation

(X denotes site of  
hydrogen exchange)

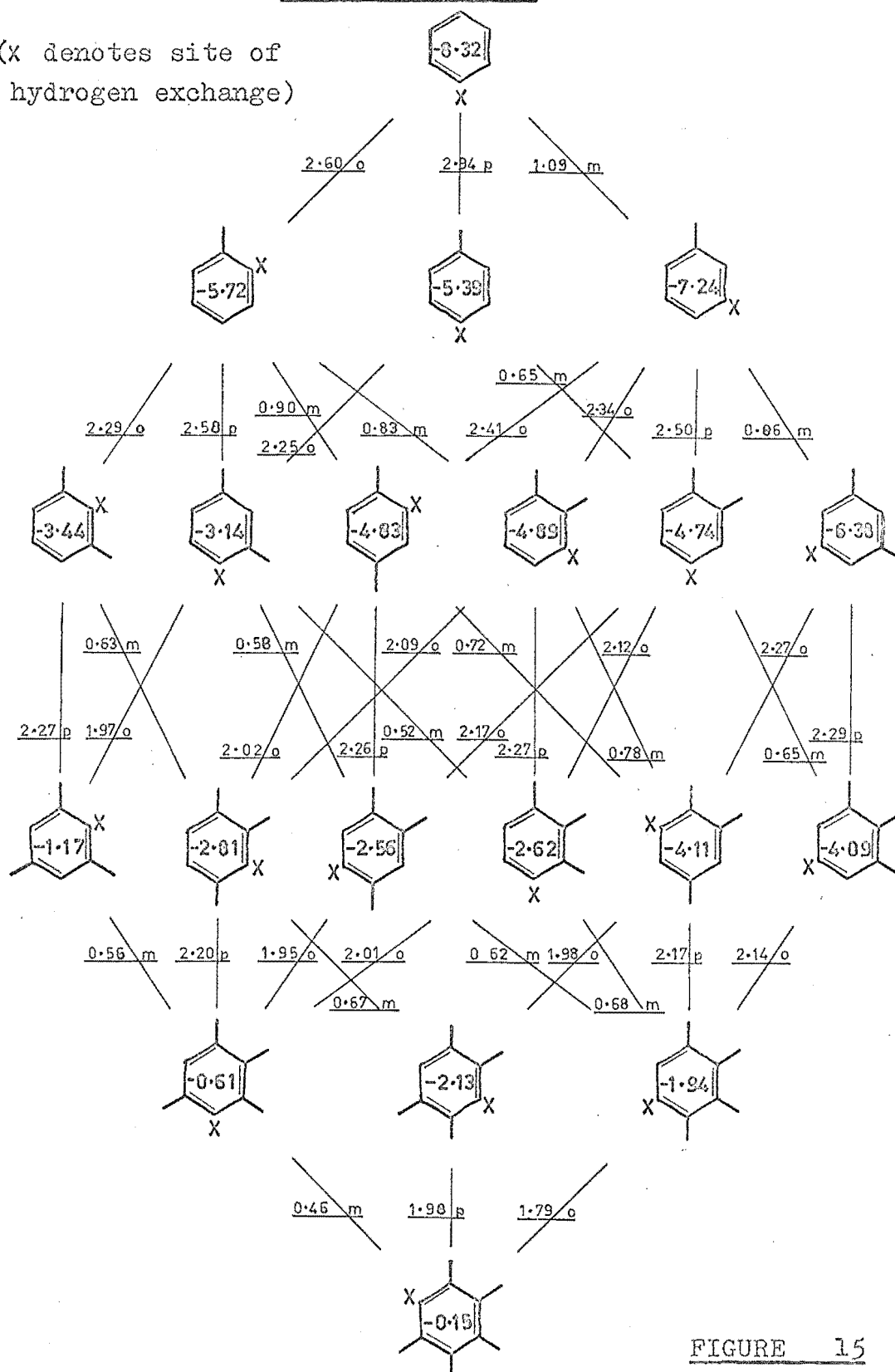


FIGURE 15

## (2) Saturation as a General Phenomenon

### (a) Introduction

Consideration of the above results prompted a reassessment of partial rate factors. Instead of being represented by a characteristic free energy increment, perhaps the substituent should be described by a proportionality constant describing the fraction of free energy of activation reduced by substitution. This description would inherently impose a "saturation" effect on the absolute magnitudes of the substituent free energy increments as the unsubstituted substrate becomes more reactive, and the activation energy becomes smaller. The proportionality constant itself was regarded as the integral of a differential equation describing the dependence of the energy of activation on infinitesimal substitution. The limits of integration defined the difference between the substituents of the two compounds whose rates were being compared. As these limits were additive, proportionality constants for multiple substitutions were easily obtained as they were also additive.

To avoid begging the question of how much of the experimental energy of activation can be affected by substituents, the energy was assumed to be separable into two parts, only one of which was influenced by substitution. A graphical method of estimating this part of the activation

energy was derived.

(b) Saturation Equations

For the reaction  $A + B_i \rightleftharpoons AB_i \rightarrow (\text{products})$  (where  $B_i$  is a series of related compounds), suppose that the activation energy is  $\Delta G_i^\ddagger$ . Part of the activation energy will represent the development of charge in the substrate  $B_i$ . If we assume that this is the part affected by substituents in  $B_i$ , and that we can separate  $\Delta G_i^\ddagger = \Delta A^\ddagger + \Delta B_i^\ddagger$ , where  $\Delta A^\ddagger$  is not changed if  $B_i$  only is changed, then for a polarisable substituent the effect on a substitution should be dependent on this charge. If it is assumed that the effect is proportional to  $\Delta B_i^\ddagger$ , then a characteristic substituent parameter,  $S$ , can be defined such that

$$d(\Delta B_i^\ddagger) = -\Delta B_i^\ddagger \cdot dS \quad \begin{array}{l} \text{(Change in activation} \\ \text{energy for infinitesimal} \\ \text{change in substitution. )} \end{array}$$

∴ for finite substituent constants,

$$\Delta B_2^\ddagger / \Delta B_1^\ddagger = e^{-\Delta S_{1,2}}$$

represents the effect of adding the substituent, characterized by the quantity  $\Delta S_{1,2}$ , which converts  $B_1$  into  $B_2$ .

Also  $\log_e k = C - \Delta G^\ddagger / RT$

( $C = \log_e kT/h$  from  
absolute rate theory)

$$\begin{aligned} \therefore \log(k_2/k_1) &= [-1/2.303RT] \cdot [\Delta G_2^\ddagger - \Delta G_1^\ddagger] \\ &= [\Delta B_1^\ddagger / 2.303RT] \cdot [1 - e^{-\Delta S_{1,2}}] \quad (\text{if } \Delta A^\ddagger, T \text{ are constant}) \\ &= \rho_1 \sigma_{12} \quad (\text{with nomenclature by analogy with the Hammett equation}^{90}) \end{aligned}$$

This equation shows that  $\rho$  will be smaller as the activation energy becomes smaller. This is consistent with the accepted view that selectivity depends on the demand placed on the substituent. The equation also predicts that multiple substitution will not produce an additive effect because of the dependence on  $(1 - e^{-\Delta S_{1,2}})$  rather than  $\Delta S_{1,2}$ .

Also 
$$\Delta S_{1,2} = \sum_j^n S_j$$

where  $1, \dots, j, \dots, n$  are the substituents required to convert  $B_1$  into  $B_2$ .

Let  $B_H$  denote the unsubstituted compound of a series. For any other two compounds:-

$$\begin{aligned} \log(k_2/k_1) &= \log(k_2/k_H) - \log(k_1/k_H) \\ &= [\Delta B_H^\ddagger / 2.303RT] \cdot [e^{-\Delta S_{H,1}} - e^{-\Delta S_{H,2}}] \\ &= \rho_H [1 - e^{-\Delta S_{1,2}}] \cdot [e^{-\Delta S_{H,1}}] \end{aligned}$$

and  $\log(k_1/k_H) = \rho_H [1 - e^{-\Delta S_{H,1}}]$

$$\begin{aligned}\therefore \log(k_2/k_1) &= [\rho_H - \log(k_1/k_H)] \cdot [1 - e^{-\Delta S_{1,2}}] \\ &= \rho_1 \sigma_{12} \\ \therefore \rho_1 &= [\rho_H - \log(k_1/k_H)] .\end{aligned}$$

$$\text{Also } \log(k_2/k_1) = -\sigma_{12} \log k_1 + \sigma_{12}(\rho_H + \log k_H)$$

so that a plot of  $\log(k_2/k_1)$  against  $\log(k_1)$  for  $B_1 \rightarrow B_2$  representing addition of a given substituent has slope  $-\sigma_{12}$  and intercept  $\sigma_{12}(\rho_H + \log k_H)$ . This means that if two series of compounds undergo a given reaction, and members of the second series (2) are obtained from those of the first (1) by addition of a given substituent ( $\sigma_{12}$ ) then the relationship between (1) and (2) is given by the above equation, and a plot of the data for each related pair of compounds should be a straight line.

### (3) Application of the Saturation Equations to Detritiation

Plots of  $\log(k_2/k_1)$  against  $\log(k_1)$  were examined for the addition of o, m, and p methyl groups in the detritiation of the polymethylbenzenes, and clearly showed a non-zero slope. The points show considerable scatter (Figures 16-18) but also a clear trend with the greatest deviation being  $0.22 \log_{10}$  units. Results are shown in Table 15.

The ratios of Intercept / Slope are shown in Table 16.

The correlations shown in these two tables have interesting consequences in the light of our theory.

FIGURE 16

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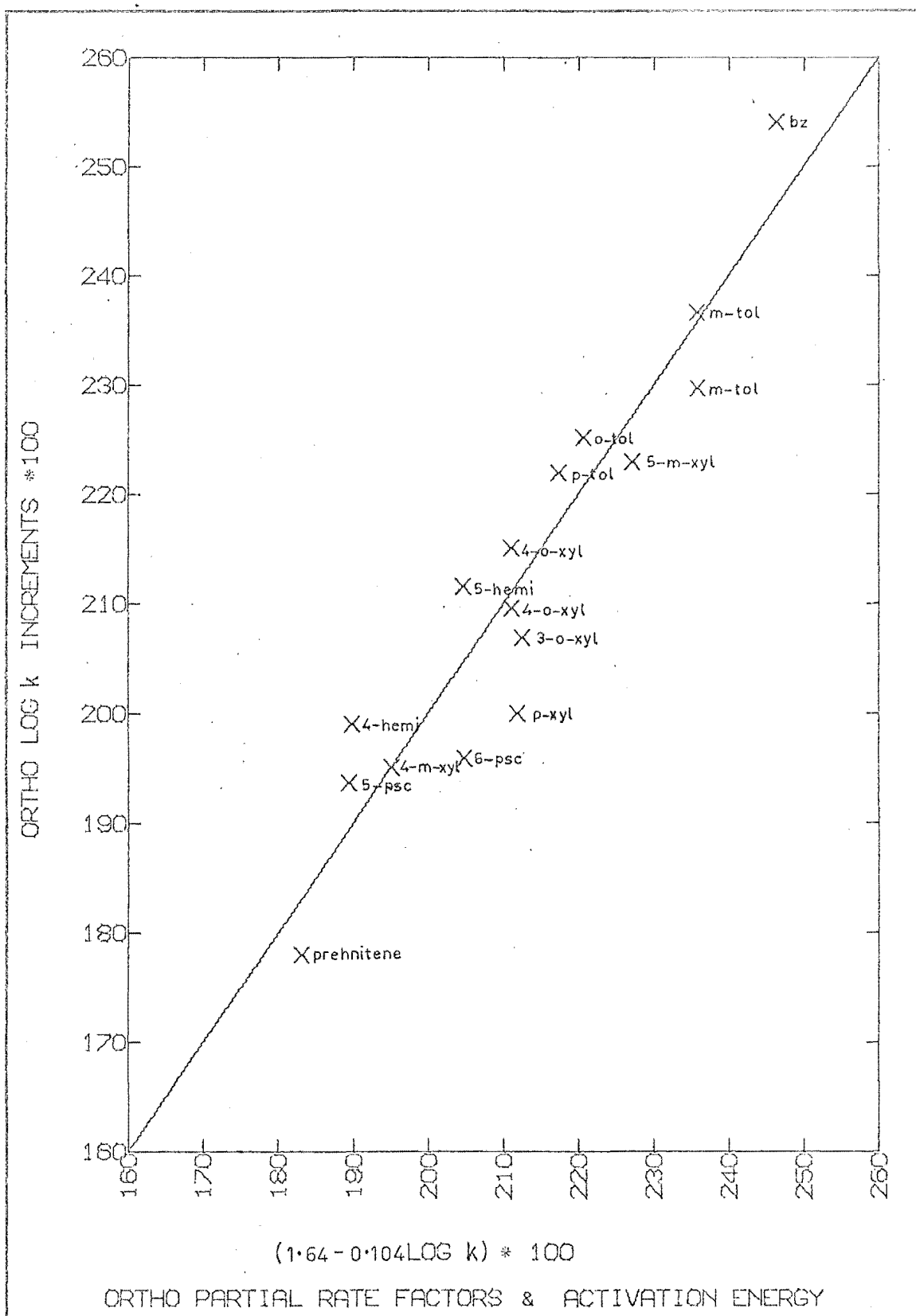




FIGURE 17

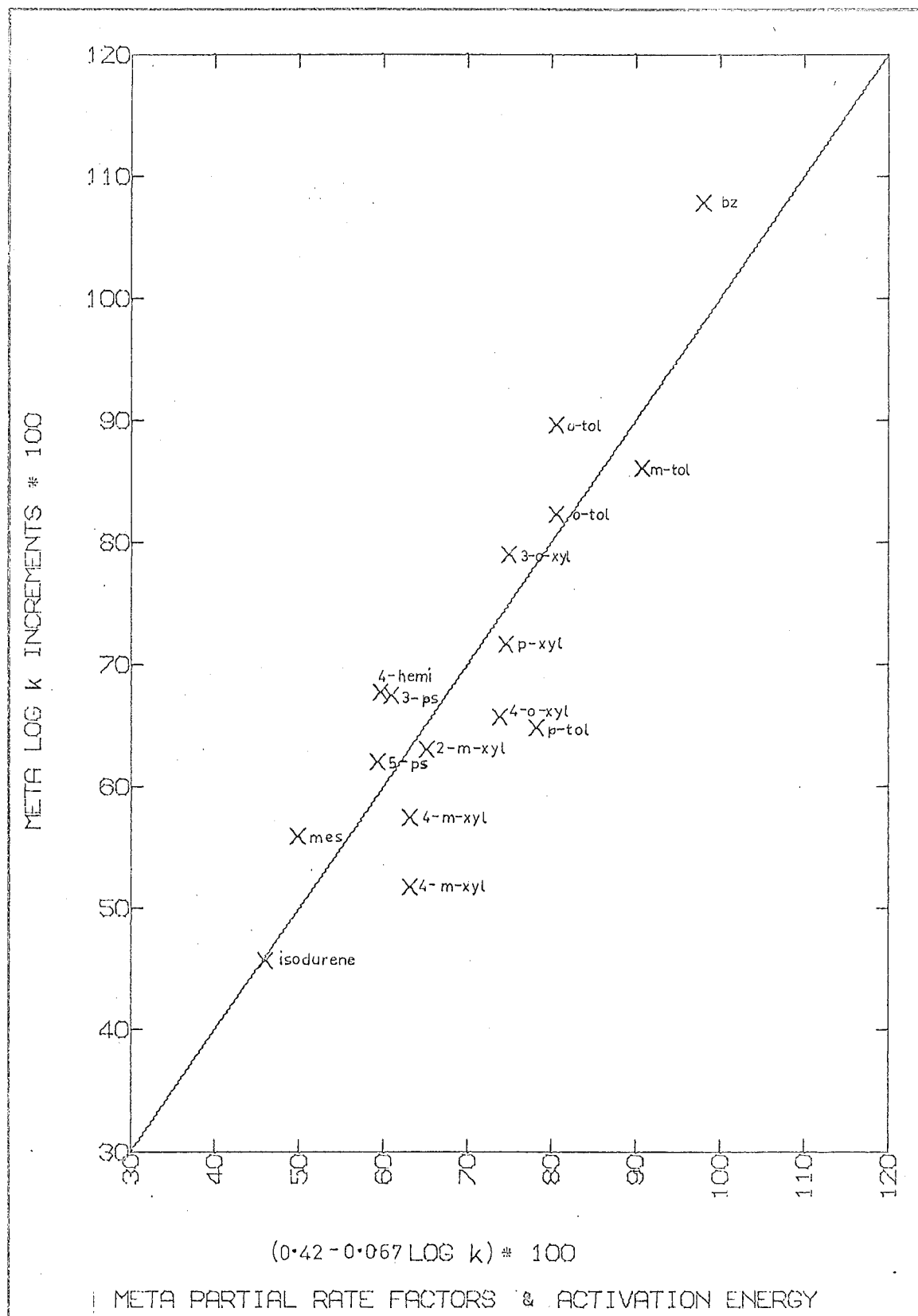


FIGURE 18

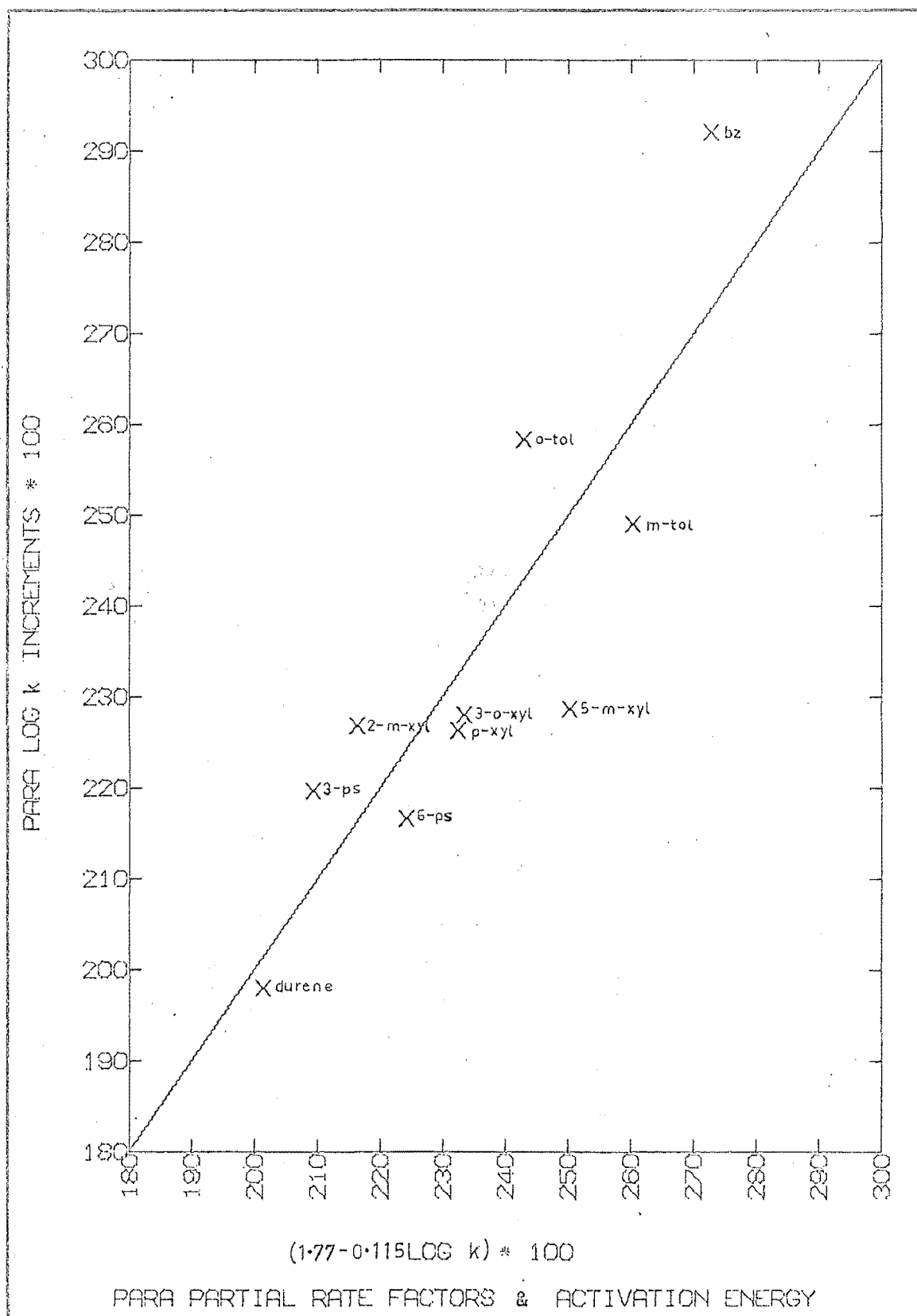


TABLE 15

Parameters Obtained From Plots of  $\Delta \log k$  Against  $\log k$  forAddition of Substituents in Detritiation

<u>Methyl Position</u>	<u>Slope<sup>a</sup></u>	<u>Error</u>	<u>Intercept</u>	<u>R<sup>b</sup></u>	<u>Error of Estimate</u>
o	-0.104	0.010	1.640	0.944	0.069
m	-0.067	0.009	0.420	0.888	0.075
p	-0.115	0.024	1.768	0.864	0.140

(a) The plot is of the form

$$\Delta \log k = (\text{slope}) \cdot \log k + \text{intercept}.$$

(b) Multiple Correlation Coefficient.

Firstly, the ortho and para correlations do have a constant intercept / slope ratio, with a value slightly larger than that predicted from the absolute rate equation.

$$\left[ (k = (kT/h) \cdot \exp(-\Delta G^\ddagger / RT)) \right]$$

$$\text{intercept/slope} = -(\rho_H + \log k_H) = -(\Delta B_H^\ddagger / 2.303RT + \log k_H)$$

(page 114)

$$= -\log (kT/h)$$

$$\text{if } \Delta B_H^\ddagger = \Delta G_H^\ddagger$$

$$= -12.80$$

if the whole of the

activation energy is dependent on the substituent effect, ( $\Delta A^\ddagger = 0$ ), and  $k_H$  has units  $\text{sec}^{-1}$ . ]

However, the meta ratio is substantially (and statistically significantly) below this value, representing a greater degree of saturation than for the other positions. This

TABLE 16

Inter-relation Between Parameters of Table 15.

<u>Methyl Position</u>	<u>Intercept/Slope</u>	<u>Estimates of Standard Error</u>		
		(a)	(b)	(c)
ortho	-15.8	1.6	+1.8	-2.1
meta	-6.3	1.1	+1.4	-1.7
para	-15.3	3.3	+3.5	-5.5

(a) Calculated from the approximate relationship;<sup>91</sup>

$$\left[ \frac{\sigma_{A/B}}{(A/B)} \right]^2 = \left[ \frac{\sigma_A}{A} \right]^2 + \left[ \frac{\sigma_B}{B} \right]^2$$

where A and B are the means of two independent variables, (A/B) is the mean of the indicated quotient, and for both A and B the probability of a value close to zero is very small. This relationship does not allow for the covariance between slope and intercept. (b) and (c) allow for an extreme case, and show the asymmetry of the distribution of the quotient.

(b) Assumes worst covariance (-1) for positive deviations.

(c) Assumes worst covariance (-1) for negative deviations.

could be explained in terms of this theory, as a result of the isolation of meta substituents from the resonance system of the ring. It is interesting to note that it has been observed that  $\rho_m$  is not necessarily equal to  $\rho_p$  for a given reaction.<sup>92</sup> Such effects could occur when the part of the free energy of activation which is accessible to a meta substituent, is modified.

Other significant features of the plots are that there is an overall pattern of deviations imposed upon this general saturation trend. The same compounds appear in similar positions on all three graphs, and this factor, rather than experimental error, must account for much of the scatter. Also, the para plot is clearly worse than the others which could indicate that this position is the major cause of deviations from additivity other than simple saturation.

#### (4) Partition of Activation Energy

The meta substituents can modify only a small part of the activation energy, and we can subdivide the total energy  $\Delta B_i^\ddagger$  into two parts,  $\Delta M_i^\ddagger$  and  $\Delta R_i^\ddagger$ , say, where the first part only can be affected by meta substitution. The question of how these two parts are modified by substituents in the other positions is crucial to a consistent theory.

Each substituent now requires two S parameters ( $\Delta S^M$ ,  $\Delta S^R$ ) and

$$d(\Delta B_i^\ddagger) = -\Delta M_i^\ddagger \cdot dS^M - \Delta R_i^\ddagger \cdot dS^R$$

and if they can be separated:-

$$\Delta M_2^\ddagger / \Delta M_1^\ddagger = e^{-\Delta S_{1,2}^M}$$

$$\Delta R_2^\ddagger / \Delta R_1^\ddagger = e^{-\Delta S_{1,2}^R}$$

$$\begin{aligned} \Delta B_2^\ddagger - \Delta B_1^\ddagger &= -2.303RT \log(k_2/k_1) \\ &= -\Delta M_1^\ddagger (1 - e^{-\Delta S_{1,2}^M}) + \Delta R_1^\ddagger (1 - e^{-\Delta S_{1,2}^R}) \end{aligned}$$

$$\begin{aligned} \therefore \log(k_2/k_1) &= (\Delta M_1^\ddagger / 2.303RT) (1 - e^{-\Delta S_{1,2}^M}) + \\ &\quad (\Delta R_1^\ddagger / 2.303RT) (1 - e^{-\Delta S_{1,2}^R}) \\ &= \rho^M \cdot \sigma_{12}^M + \rho^R \cdot \sigma_{12}^R \quad \text{by analogy with the} \\ &\quad \text{Taft relationship.}^{20} \end{aligned}$$

As before, we may relate this increment to the unsubstituted compound designated H.

$$\begin{aligned} \log(k_2/k_1) &= \log(k_2/k_H) - \log(k_1/k_H) \\ &= \rho_H^M (1 - e^{-\Delta S_{1,2}^M}) (e^{-\Delta S_{H,1}^M}) + \rho_H^R (1 - e^{-\Delta S_{1,2}^R}) (e^{-\Delta S_{H,1}^R}) \\ &= \rho_H^M \cdot \sigma_{12}^M (1 - \sigma_{H1}^M) + \rho_H^R \cdot \sigma_{12}^R (1 - \sigma_{H1}^R) \end{aligned}$$

For  $B_2$  and  $B_1$  differing only by a meta group  $\sigma_{12}^R = 0$

$$\text{and } \log(k_2/k_1) = \rho_H^M \cdot \sigma_m^M (e^{-\Delta S_{H,1}^M})$$

where  $\sigma_m^M$  is the constant for a single meta group.

$$\text{or } \log_e(\log(k_2/k_1)) = c - \Delta S_{H,1}^M$$

$$\text{where } c = \log_e(\rho_H^M \cdot \sigma_m^M)$$

If  $\Delta M^\ddagger$  is considered to be due to charge localisation at the positions meta to the reaction site, then there may be two ortho effects corresponding to different positions relative to a particular meta position.

The data shown in Figure 17 was re-analysed in terms of substitution in the various other positions around the ring.

$$\text{i.e. } \log_e(\log(k_2/k_1)) = \beta_1 n_o + \beta_2 n_o + \beta_3 n_m + \beta_4 n_p + \beta_5$$

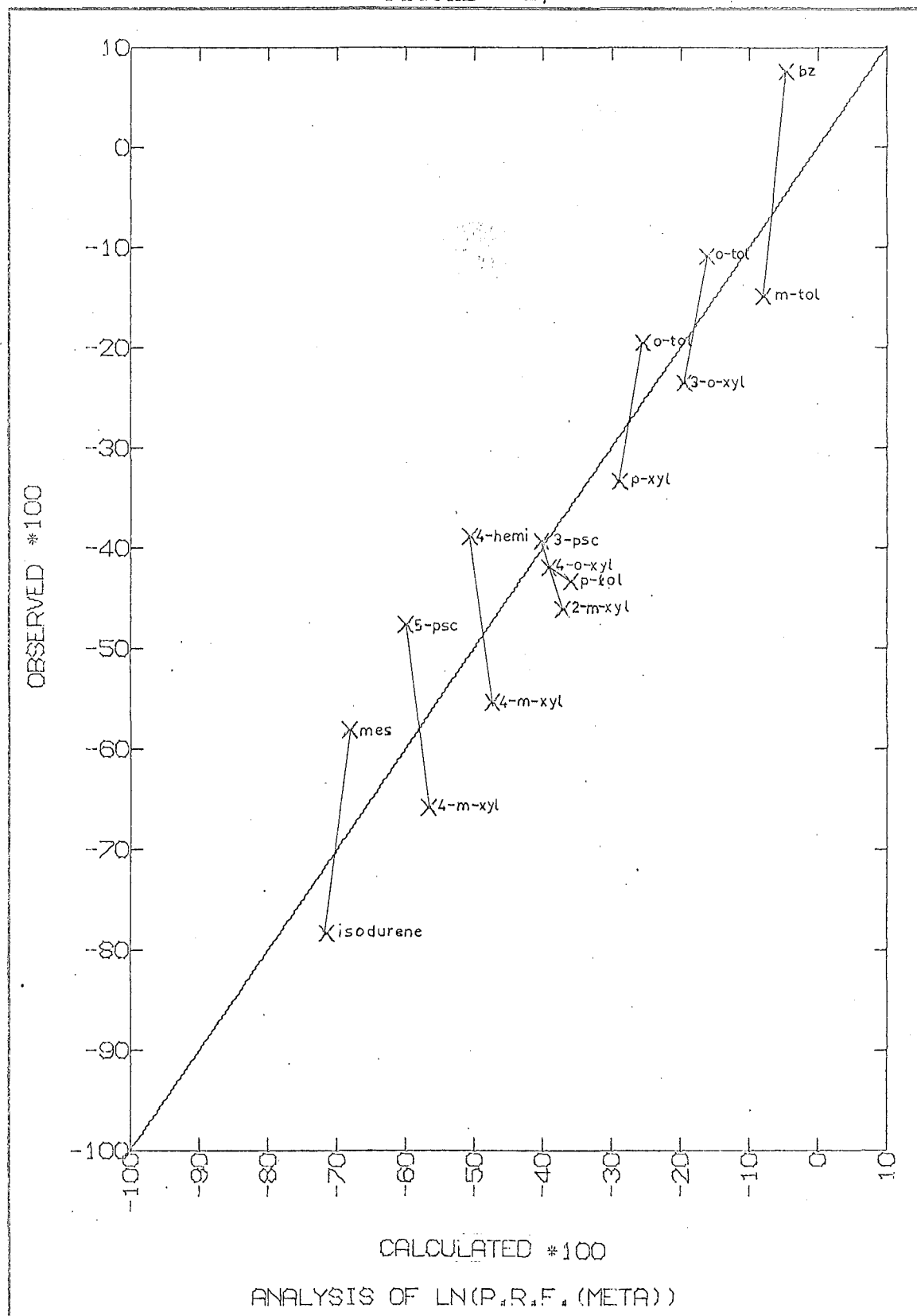
where  $n_o$  is the number of methyl groups ortho to the reaction site, and adjacent to the meta methyl group whose effect is represented by  $k_2/k_1$ .  $n_o$ ,  $n_m$ ,  $n_p$  represent similar quantities for the other positions, and the regression coefficients are designated  $\beta$ . From the relation above:

$$\beta_5 = c = \log_e(\rho_H^M \cdot \sigma_m^M) \quad (\text{See page 122})$$

$\beta_1, \dots, \beta_4$  are the  $\Delta S^M$  values for methyl substitution at the indicated positions. Results are shown in Table 17, and Figure 19.

The standard error of the estimate represents an 11% error in  $\log_{10}(k_1/k_2)$  for meta substitution which is about 0.07  $\log_{10}$  units. This corresponds to an 11% error in the ratio  $k_2/k_1$  which could be produced by 8% errors in the rate-constants  $k_1$ ,  $k_2$ . However, this standard error is little smaller than that for the simple saturation theory shown in Table 15 where the error was 0.075  $\log_{10}$  units

FIGURE 17





for the same data using two parameters (slope and intercept) to predict the increment produced by meta substitution given the rate-constant of the unsubstituted compound. This indicates that the reactivity of the "unsubstituted" compound is a good guide to the increment to be expected from addition of a meta methyl substituent. Note also the similarity between Figures 17 and 19.

TABLE 17

Regression Analysis of Substituent Effects for the Activation  
Energy Accessible to Meta Methyl Groups

<u>Other Substituents<sup>a</sup></u>	<u><math>\Delta S_x^M</math></u>	<u>S.E. of <math>\Delta S_x^M</math></u>	<u>T-Value<sup>b</sup></u>
Adjacent ortho (o )	0.208	0.048	4.31
Para (p)	0.312	0.048	6.44
Opposite ortho (o)	0.115	0.048	2.37
Opposite meta (m)	0.003	0.005	0.68
Intercept	-0.0475		
Multiple Regression Coefficient		0.907	
Standard Error of Estimate		0.108	

(a) Ortho, meta, and para are relative to the reaction site. Opposite and adjacent are relative to the meta methyl group whose effect is being studied.

(b) For 11 degrees of freedom.

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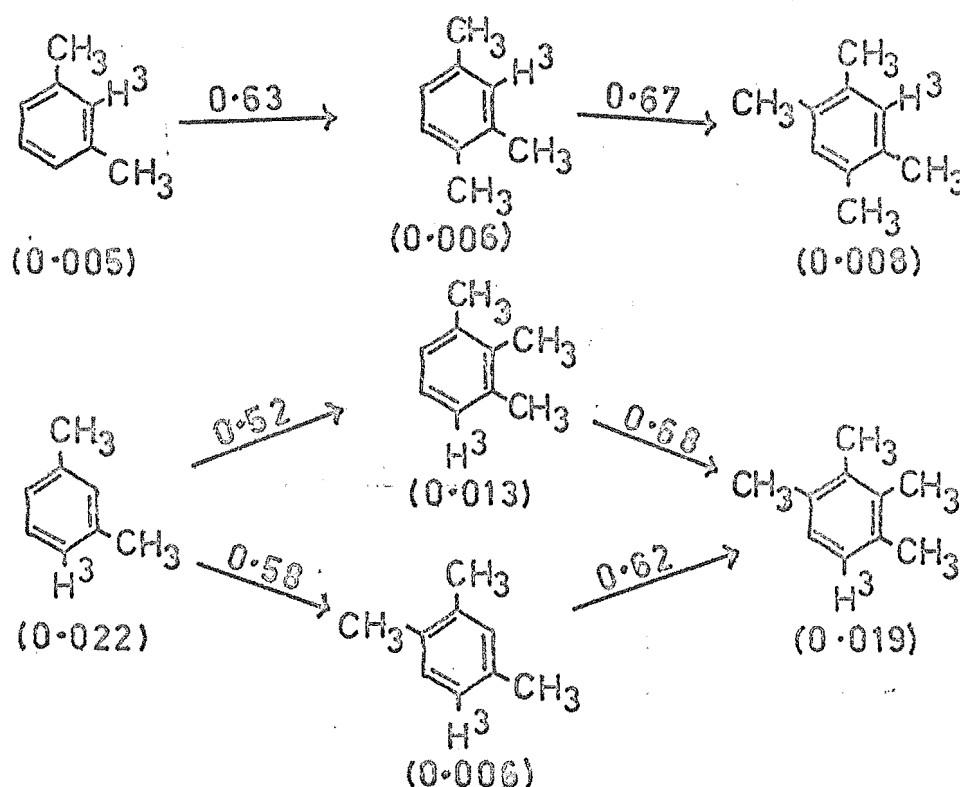
The lines in Figure 19 connect compounds related by a meta methyl group. It is seen that the two and four positions of m-xylene are the basic cause of the large error, as the first methyl group inserted meta to these positions

has a smaller effect than the second contrasting with the otherwise general tendency for effects to become smaller as the reactivity increases.

These peculiar increments are shown below:-

$\Delta \log_{10} k$  Increments and Estimated Experimental Errors

(in Brackets)



While experimental error could account for the bottom sequence, the others appear to be more secure. No simple explanation appears to account for these deviations.

The results of Table 17 show that there is negligible interaction between meta group effects. This justifies a separation of  $\Delta M^*$  into two parts, one for each side of the

benzene ring divided by a line passing through the para position and the centre of the ring. Designating the sides X and Y our equations become:-

$$\log(k_2/k_1) = \rho_1^M \cdot (\sigma_{12}^{MX} + \sigma_{12}^{MY}) + \rho_1^R \cdot \sigma_{12}^R$$

$$\text{and } \log(k_2/k_1) = \rho_H^M \left[ \sigma_{12}^{MX} \cdot e^{-\Delta S_{H,1}^{MX}} + \sigma_{12}^{MY} \cdot e^{-\Delta S_{H,1}^{MY}} \right]$$

$$+ \rho_H^R \cdot \sigma_{12}^R \cdot e^{-\Delta S_{H,1}^R}$$

The fact that  $\Delta S_m^{MY}$  appears to be zero for meta methyl substitution on the X side (see Table 17 ) means that

$$\sigma_m^{MY} = (1 - e^{-\Delta S_m^{MY}}) = 0$$

$$\text{and so } \log(k_2/k_1) = \rho_H^M \cdot \sigma_{12}^{MX} \cdot e^{-\Delta S_{H,1}^{MX}}$$

which justifies the form of the equation used for the analysis (page 123).

#### (5) Values of Theoretical Constants and Correlations for Detritiation Data

The values previously listed in Table 17 define the following constants for the  $\Delta M^\ddagger$  part of the activation energy accessible to meta substituents:-

<u>Substitution</u>	<u><math>e^{-\Delta S^{MX}}</math></u>	<u><math>\sigma^{MX}</math></u>	<u><math>e^{-\Delta S^{MY}}</math></u>	<u><math>\sigma^{MY}</math></u>
<u>in Side X</u>				
ortho	0.811	0.189	0.897	0.108
meta	(0.550)	(0.450)	1.000	0.000
para	0.732	0.268	0.732	0.268

$$\text{From the intercept; } \rho_H^M \cdot \sigma_{Hm}^{MX} = 0.935$$

The values for the meta position (shown in brackets) had to be derived from other data; the slopes shown in Table 15 were taken as rough guides for  $\sigma_{Ho}^R$  and  $\sigma_{Hp}^R$ , allowing  $\rho_H^M$  and  $\rho_H^R$  to be determined from the intercept equation (above), and from rate-constants for the hemimellitenes and mesitylene. After slight modifications the following constants were obtained:-

$\rho_H^M$	$\rho_H^R$	$\frac{e^{-\Delta S_{Ho}^R}}{}$	$\sigma_{Ho}^R$	$\frac{e^{-\Delta S_{Hp}^R}}{}$	$\sigma_{Hp}^R$
1.7	19.0	0.890	0.110	0.893	0.107

The correlation obtained with these values is shown in Table 18 (d), and allows a standard error of 0.075  $\log_{10}$  units or about 19% of  $k$ . This could probably be reduced somewhat by least-squares refinement, but as has already been pointed out the data contains features not explicable by this theory. The correlation is substantially better than that for additivity (b), and the simple saturation theory (c) whose standard errors are over 50%.

If we assume that the total activation energy is given by

$$\Delta G_H^\ddagger = \Delta MX_H^\ddagger + \Delta MY_H^\ddagger + \Delta R_H^\ddagger$$

$$\begin{aligned} \therefore \log(kT/h) &= (\Delta G_H^\ddagger / 2.303RT) + \log k_H \\ &= 2\rho_H^M + \rho_H^R + \log k_H \\ &= 14.1 \end{aligned}$$

this is in very good agreement with the theoretical value

TABLE 18

Comparison of Substituent Effects Predicted by Simple  
Additivity and by the Saturation Equations

<u>Compound</u>	<u>Log(k)<sup>a</sup></u>	<u>Obs-Cal<sub>c</sub></u>	<u>Obs-Cal<sub>c</sub></u>	<u>Obs-Cal<sub>c</sub></u>
	Obs	Calc <sup>b</sup>	Calc <sup>c</sup>	Calc <sup>d</sup>
H <sup>3</sup> -benzene	-8.32	-0.47	+0.01	0.0
o-H <sup>3</sup> -toluene	-5.72	-0.05	0.0	0.0
m-H <sup>3</sup> -toluene	-7.24	-0.12	+0.09	+0.15
p-H <sup>3</sup> -toluene	-5.39	+0.10	0.0	0.0
3-H <sup>3</sup> -o-xylene	-4.89	+0.05	-0.04	+0.09
4-H <sup>3</sup> -o-xylene	-4.74	+0.02	-0.22	-0.05
2-H <sup>3</sup> -m-xylene	-3.44	+0.06	0.0	0.0
4-H <sup>3</sup> -m-xylene	-3.14	+0.18	0.0	+0.01
5-H <sup>3</sup> -m-xylene	-6.38	+0.01	0.0	+0.07
2-H <sup>3</sup> -p-xylene	-4.83	+0.11	-0.03	+0.06
4-H <sup>3</sup> -hemimellitene	-2.62	-0.03	-0.23	-0.03
5-H <sup>3</sup> -hemimellitene	-4.09	-0.06	-0.39	-0.09
3-H <sup>3</sup> -pseudocumene	-2.81	-0.04	-0.14	-0.05
5-H <sup>3</sup> -pseudocumene	-2.56	+0.03	-0.17	-0.03
6-H <sup>3</sup> -pseudocumene	-4.11	+0.10	-0.10	+0.03
2-H <sup>3</sup> -mesitylene	-1.17	-0.03	0.0	0.0
5-H <sup>3</sup> -prehnitene	-1.94	-0.08	-0.27	+0.04
4-H <sup>3</sup> -isodurene	-0.61	-0.20	-0.10	+0.06
3-H <sup>3</sup> -durene	-2.13	-0.07	-0.19	-0.05
6-H <sup>3</sup> -pentamethyl- benzene	-0.15	-0.47	-0.27	+0.02
Standard Error		0.17	0.18	0.075
(corrected for degrees of freedom)				

(Table continued on next page.)

TABLE 18 (continued)

(a)  $k$  is rate-constant for detritiation in trifluoroacetic acid at  $70.0^{\circ}\text{C}$ .

(b) Least squares analysis assuming additivity of log (partial rate factors).

(c) Simple saturation equation assuming  $\rho_{\text{H}} = \Delta G_{\text{H}}^{\ddagger} / 2.303RT$  and taking  $\sigma_{\text{Ho}} = 0.123$ ,  $\sigma_{\text{Hm}} = 0.0472$ ,  $\sigma_{\text{Hp}} = 0.139$ , so as to agree with the toluene and m-xylene results.

(d) Partitioned saturation equation. See page 122.

of 12.9, and is evidence for the validity of the assumption that substituent effects (for methyl groups at least), are directly proportional to the free energy of activation. Peculiar features of these correlation constants are that ortho and para substitutions affect the major part of the activation energy almost identically, and the unequal distribution is the result of the small (about 18%) part accessible to meta substituents which is relatively quickly "saturated". This may throw new light on the question of ortho-para ratios.

This minor part of the activation energy is efficiently reduced by methyl substituents as evidenced by the large values of  $\sigma^M$  compared with  $\sigma^R$ .

#### (iv) Molecular Orbital Calculations

Reactivity indices derived from various molecular orbital models have been reviewed by Greenwood and McWeeney,<sup>93</sup> and considerable progress has been made with more sophisticated treatments as more powerful computing facilities become available.

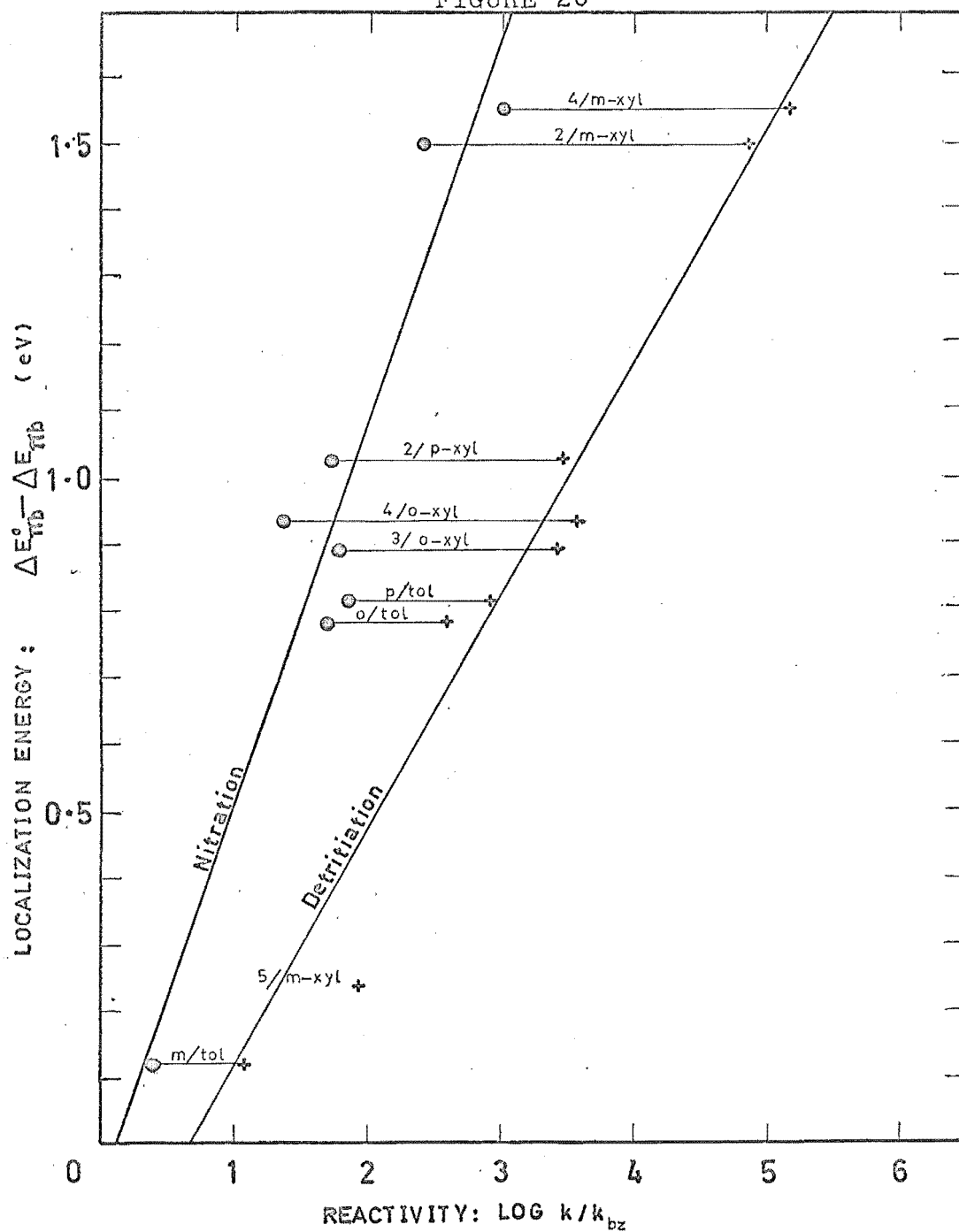
Figure 20 shows the comparison between the rates of detritiation and localisation energies calculated by Clark and Fairweather using the Pariser-Parr-Pople self-consistent field method. They treated the methyl group as a pseudo-hetero-atom and parameters for mesomeric, and both  $\sigma$  and  $\pi$  inductive interactions were found necessary to achieve correlation with their results for nitration, also shown in Figure 20.<sup>94</sup>

General trends are reproduced but deviations are evident. The effect of meta substitution is severely underestimated and the buttressing second order effect (page 96) is overestimated. (The 3 position of o-xylene is almost as reactive as one position of p-xylene, whereas the calculated values differ considerably.)

Nitration is a more complex reaction than hydrogen exchange, and it has been shown that acetoxylation accompanies nitration in nitric acid/acetic anhydride mixtures.<sup>1,95</sup> The present nitration results obtained by Clark and Fairweather using nitric acid/acetic acid must be regarded with caution as long as the factors



FIGURE 20



'P.R.P.' MOLECULAR ORBITAL LOCALIZATION ENERGIES

controlling product ratios of nitration and acetoxylation in the polymethylbenzenes in similar systems are still not understood.

Several earlier molecular orbital calculations for the basicities of the polymethylbenzenes have been reviewed by Perkampus.<sup>96</sup> Inductive contributions from the methyl groups appeared to be more important than hyperconjugation.

(B) N.M.R. Spectra of Polymethylbenzenes

A number of studies of the N.M.R. spectra of the methylbenzene series has been made, but few have covered the complete range of compounds.<sup>39,40,41,42</sup> It appears that some erroneous interpretations may have been made of this incomplete data.

The spectra show sharp unsplit methyl peaks for all compounds except pentamethylbenzene for which two methyl groups appear to lie under a rather broader peak. The aromatic protons, although strongly coupled, show almost single peaks for all compounds, and these were taken to represent the mean positions of the actual chemical shifts. For m-xylene the smaller peaks were more significant. The solvent effects correlation compared only the large ring proton peak for each compound. Details of measurements and results of this thesis have been described earlier. (See pages 77-81) Assignments of methyl peaks are discussed in Section (ii)(1).

(i) Solvent Effects

(1) Correlations

Figures 21 and 22 show chemical shifts in  $\text{CCl}_4$  compared with those in n-hexane for both ring and methyl protons for the whole series of polymethylbenzenes by least squares analyses using program STEPR (page 58 ), and the relation

$$\tau_{\text{CCl}_4} = m \cdot \tau_{\text{n-hexane}} + \tau_0 \quad \text{Correlation parameters}$$

TABLE 19

Solvent Shifts ( $\tau_{\text{CCl}_4} - \tau_{\text{n-hexane}}$ ) for Polymethylbenzene Protons

Relative to Toluene Shifts

<u>Compound</u>	<u>Methyl Protons<sup>a</sup></u>	<u>Ring Protons<sup>b</sup></u>
Benzene		-0.03
Toluene	0.0	0.0
o-Xylene	0.01	0.02
m-Xylene	0.01(5)	0.04
p-Xylene	0.0	0.0
Hemimellitene	0.01(5)	0.01
Pseudocumene	0.02	0.03
Mesitylene	0.02(5)	0.03
Prehnitene	0.03(5)	0.05
Isodurene	0.03(5)	0.05
Durene	0.02(5)	0.04
Pentamethylbenzene	0.03	0.06
Hexamethylbenzene	0.02	

(a) Average values for polymethylated compounds.

(b) Shift for major peak only.

FIGURE 21

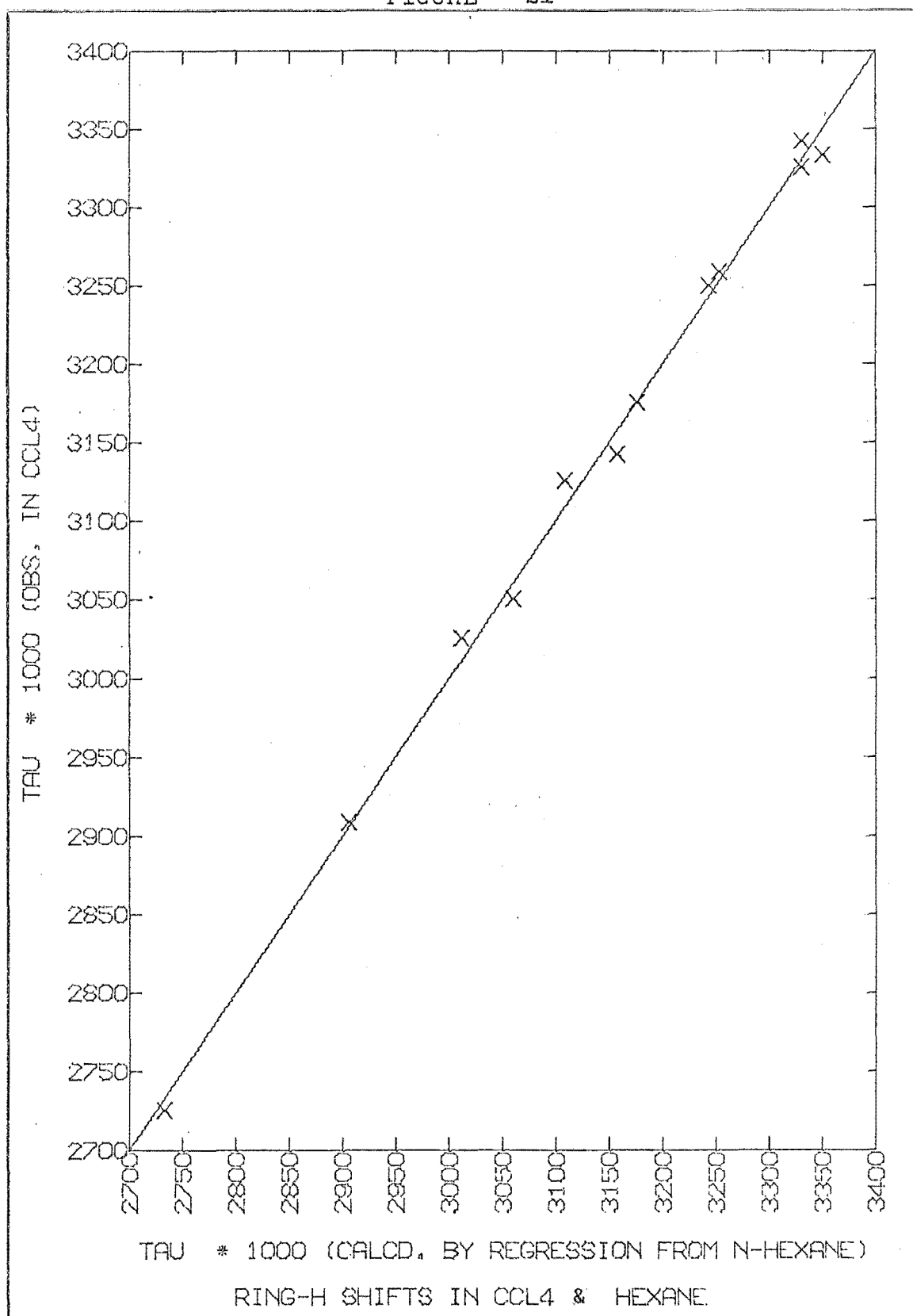
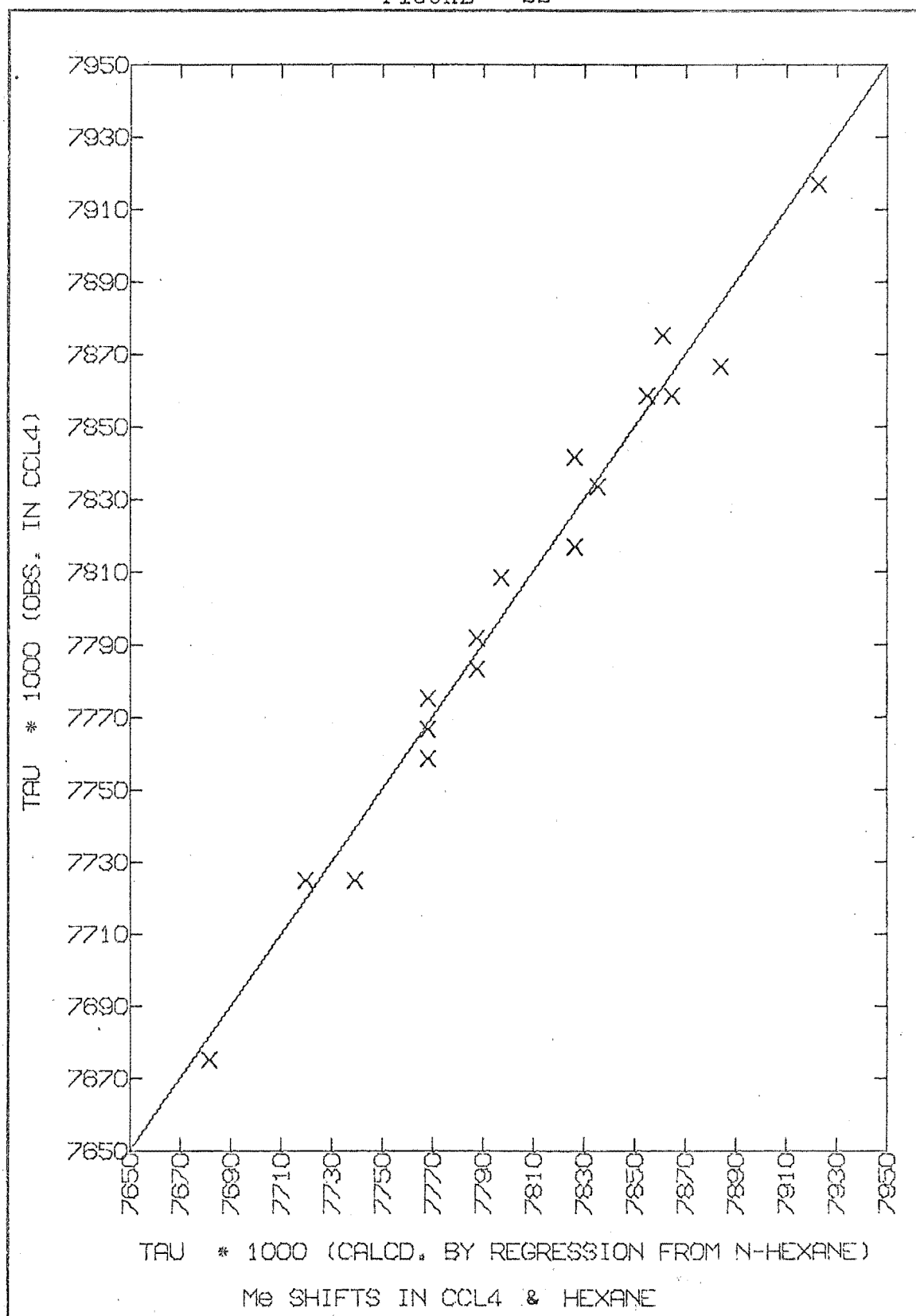


FIGURE 22



are shown in Table 20.

TABLE 20

Least Squares Analysis of Solvent Effects

	<u>Slope</u> (m)	<u>S.E. of</u> <u>Slope</u>	<u>Intercept</u> ( $\tau_0$ )	<u>S.E. of</u> <u>Estimate</u>	<u>R<sup>a</sup></u>
Ring H	1.16	0.02	-0.487	0.012	0.998
Methyl H	1.16	0.05	-1.250	0.010	0.985

(a) R is the Multiple Correlation Coefficient.

Both types of proton give excellent correlations, and therefore provide good evidence for the reliability of the measurements.

(2) Steric Effects

The results of this work are consistent with  $\text{CCl}_4$  producing a small deshielding effect which is a linear function of the chemical shift of the proton. Ronayne, Williams, and Wilson<sup>42</sup> have studied solvent effects on the aromatic proton shifts in toluene, m-xylene, p-xylene, and mesitylene for several solvents including carbon tetrachloride. They concluded that  $\text{CCl}_4$  had a large van der Waal's interaction with the solute protons which decreased along the above hydrocarbon sequence, and so was a function of the increasing steric hindrance. However, when the solvent shifts for the complete range of methyl and

ring protons are considered no deviations attributable to steric factors are discernible.

It should be pointed out that steric effects are better established for solvent shifts, such as those induced by benzene, in which relative solvent-solute positions and orientations are critical.<sup>38</sup> Nevertheless, failures to observe expected steric effects have also been noted, together with the generalisation that benzene solvent shifts indicate solvent-solute association at the group for electron donating substituents, and over the ring for electron withdrawing substituents.<sup>97</sup>

### (3) Ring Currents

It has been suggested that substitution may affect the ring current and thus the deshielding in the plane of the aromatic ring. This effect has also been suggested to account for solvent shifts in  $\text{CHCl}_3$  and  $\text{CCl}_4$  relative to  $\text{CS}_2$ .<sup>40</sup> A change in the ring current of a molecule would cause changes in shielding as a function only of proton position relative to the ring.

The solvent shifts ( $\tau_{\text{CCl}_4} - \tau_{\text{n-hexane}}$ ) are in fact identical within 0.01ppm for all methyl protons of a given compound. However, the trend for the more deshielded protons to have a slightly greater solvent shift is also followed within this restriction. The solvent shifts in Table 20 are greater for ring protons than methyl protons



and the two series correlate quite well for each compound. Ring current fluctuations should produce more than twice as large a shielding change for ring protons compared with methyl protons. The ring proton shifts are the larger, but not by as great a factor as predicted.

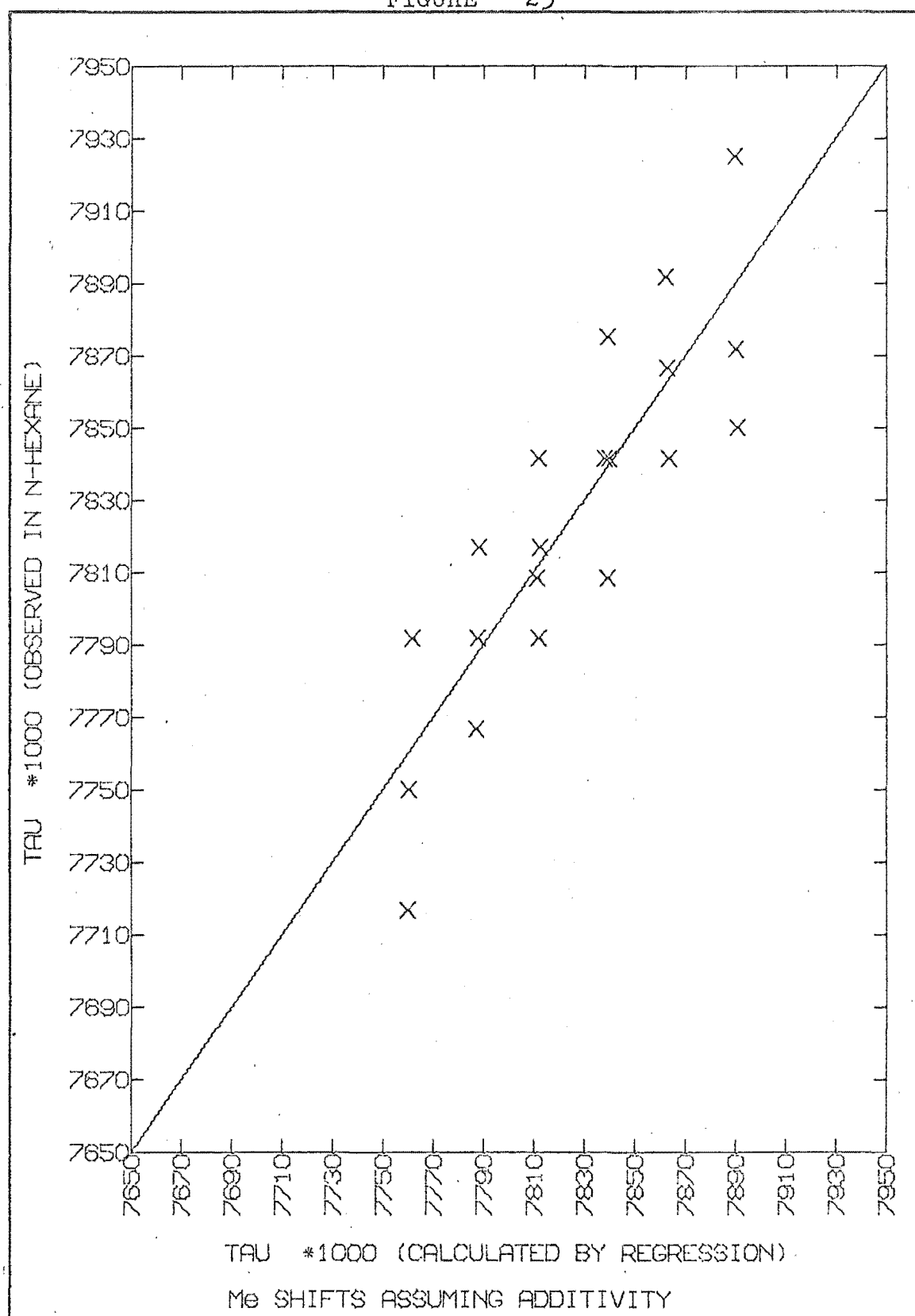
### (ii) Chemical Shifts

Chemical shifts in fluoro-aromatics have been well established as reliable estimates of inductive effects by Taft, and others.<sup>23</sup> In the absence of unaccountable anisotropy effects the chemical shifts of protons are also a reflection of their electronic environment, and may be used to picture the relatively unperturbed ground state molecule for comparison with the activated complex to which kinetic data applies. Previous work on mono, di-, and trimethylbenzenes has stressed the additivity of the chemical shifts of the methyl protons, and used them to predict ring proton shifts.<sup>39</sup>

### (1) Examination of Additivity for Methyl Proton Shifts

On inspection of the shifts for the methyl protons (Table 6) it is clear that a simple additivity relationship will not be successful. The least squares regression line is shown in Figure 23, and the parameters in Table 21, for the best fit of:-  $\tau_{n\text{-hexane}} = \beta_o n_o + \beta_m n_m + \beta_p n_p + \beta_f$

FIGURE 23



$\beta_x$  are adjustable regression coefficients, and  $n_x$  are the numbers of methyl groups at position  $x$  relative to the observed methyl group.

TABLE 21

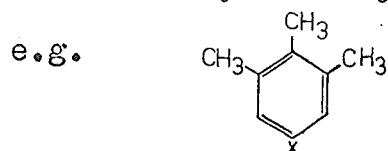
Least Squares Analysis of Additivity Assumption for Methyl  
Protons in n-Hexane<sup>a</sup>

	<u><math>\Delta \tau</math></u> (ppm)	<u>S.E. (<math>\Delta \tau</math>)</u> (ppm)	<u>T-Value<sup>b</sup></u>
ortho	0.051	0.008	6.40
meta	0.001	0.008	0.09
para	0.027	0.012	2.20
Intercept	7.760		
S.E. of Estimate	0.029		
Multiple Correlation Coefficient	0.842		

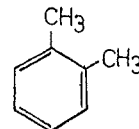
(a) Using program STEPR (Page 58)

(b) For Student's T test with 16 degrees of freedom.

We define a "flanked" methyl group as a methyl group having substituents other than hydrogen on both adjacent ring positions. A "buttressed" methyl group has a substituent on only one adjacent ring position.



A "flanked" para group  
(relative to the point of interest, x).



Two "buttressed" groups.

Examination of the shifts of the methyl protons of hemimellitene reveals that the flanked methyl group is not having a normal ortho effect on the other two. For hemimellitene peak areas allowed unequivocal assignment of the methyl peaks to the two molecular positions. For pseudocumene, prehnitene, isodurene, and pentamethylbenzene ambiguities were resolved by interpreting the largest shifts as being caused by "unflanked" ortho groups.

A number of second order interaction variables including "flanking" and "buttressing", were provided to allow STEPR to choose the most significant. The following much improved correlations were obtained. (Figure 24, Table 22.)

Statistical tests indicate that the addition of a modified value for a flanked meta position significantly improves the correlation. (Table 22 (B)) However, as this reduces the standard error of the estimate to below that of the solvent shift correlation, such refinements must be treated with caution. Modifications for flanked para groups were statistically insignificant.

## (2) Examination of Additivity for Ring Proton Shifts

Protons attached to aromatic rings are strongly coupled and the analysis of the complex spectrum is very difficult. Nevertheless, symmetry ensures that six of the methylbenzenes have only chemically equivalent ring protons. In addition the spectrum of toluene has been analysed by previous workers,<sup>98,99</sup> and by adjustment of their results to agree

TABLE 22

Least Squares Analysis of Additivity for Methyl Protons in  
n-Hexane Allowing for the Effect of Flanked Methyl Groups

(A) flanked ortho only

	<u><math>\Delta\tau</math></u> (ppm)	<u>S.E. of <math>\Delta\tau</math></u> (ppm)	<u>T-Value<sup>a</sup></u>
ortho	0.082	0.004	23.0
meta	0.031	0.004	8.8
para	0.027	0.004	7.0
ortho (fl)	0.021	0.004	5.8
Intercept	7.729		
S.E. of Estimate	0.009		
Multiple Correlation Coefficient	0.986		

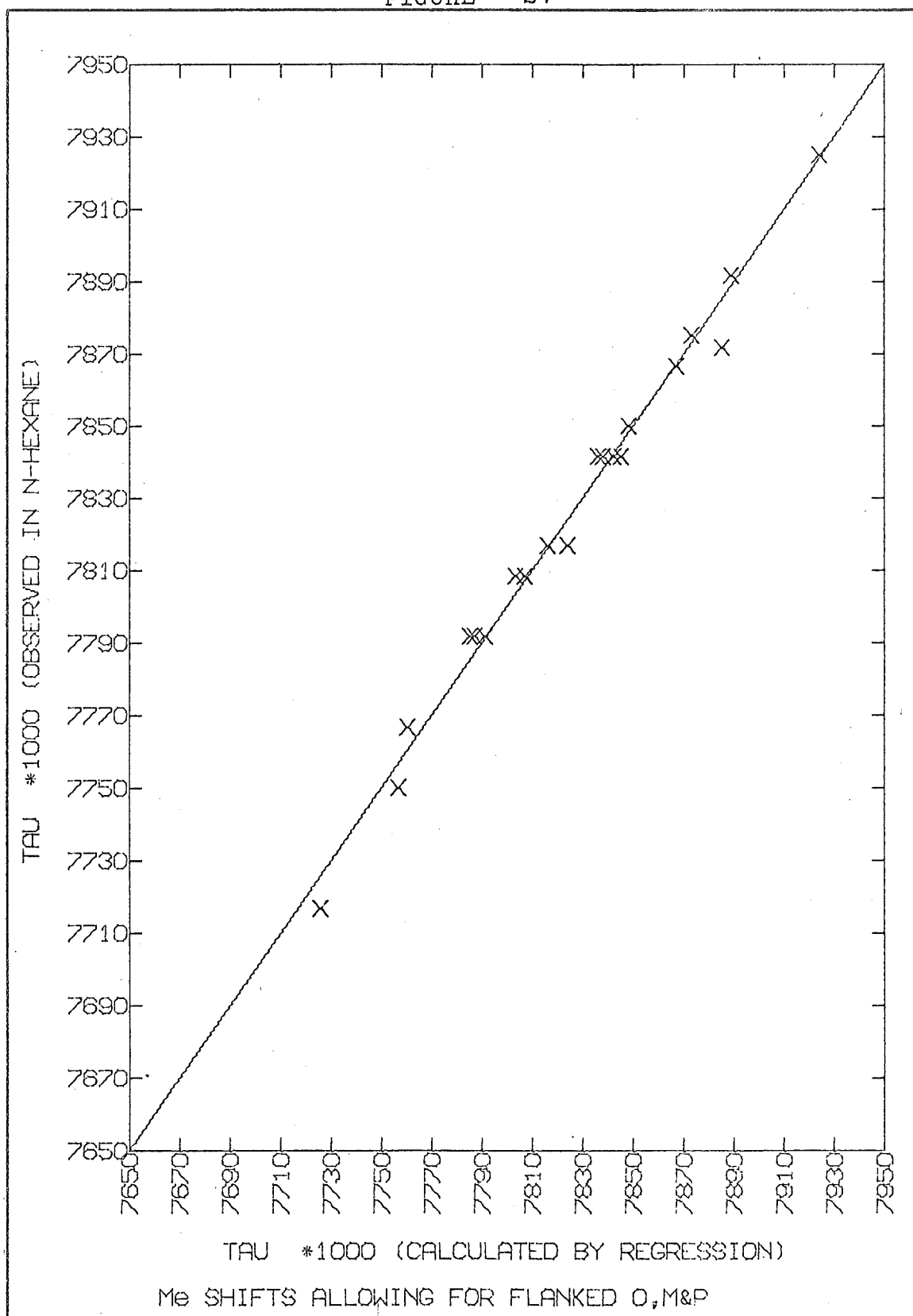
(a) 15 degrees of freedom

(B) flanked ortho and meta

	<u><math>\Delta\tau</math></u>	<u>S.E. of <math>\Delta\tau</math></u>	<u>T-Value<sup>b</sup></u>
ortho	0.082	0.003	31.8
meta	0.031	0.003	12.2
para	0.035	0.004	10.0
ortho (fl)	0.029	0.003	8.6
meta (fl)	0.015	0.004	3.8
Intercept	7.725		
S.E. of Estimate	0.007		
Multiple Correlation Coefficient	0.993		

(b) 14 degrees of freedom

FIGURE 24



with the mean position observed for toluene in this work; the following shifts relative to benzene caused by methyl substituents were derived.

$\Delta\tau$	ortho	meta	para
(ppm):	+0.18	+0.09	+0.21

These parameters were used to predict shifts for the polymethylbenzenes. Although agreement with additivity predictions is plausible for the xylenes, failure for the higher methylbenzenes is clear. (Table 23.) A much better correlation was achieved by allowing "buttressed" ortho and "flanked" meta groups to cause reduced shifts (by 0.05 and 0.07 ppm, respectively). This calculation is also shown in Table 23.

TABLE 23

Chemical Shifts ( $\tau$ ) for Ring Protons of Methylbenzenes in

<u>Position of</u> <u>Me Groups</u>	<u>n-Hexane</u>		
	<u><math>\tau</math> Obs</u>	<u><math>\tau</math> Calc<sup>a</sup></u> (Additivity)	<u><math>\tau</math> Calc<sup>b</sup></u>
	2.78	-	-
1	2.93	-	-
1,2	3.03	[3.07]	[3.04(5)]
1,3	3.11	[3.11]	[3.11]
1,4	3.07	3.05	3.05
1,2,3	3.15	[3.23]	[3.15]
1,2,4	3.17	[3.21]	[3.18]
1,3,5	3.22	3.35	3.35

(Continued next page.)

TABLE 23 (continued)

<u>Position of</u> <u>Me Groups</u>	<u>Obs</u>	<u>Calc<sup>a</sup></u> (Additivity)	<u>Calc<sup>b</sup></u>
1,2,3,4	3.23	3.35	3.23
1,2,3,5	3.30	3.44	3.32
1,2,4,5	3.23	3.32	3.22
1,2,3,4,5	3.30	3.53	3.29

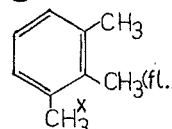
(a) Assuming  $\Delta_{\text{ortho}} = 0.18$ ,  $\Delta_{\text{meta}} = 0.09$ ,  $\Delta_{\text{para}} = 0.21$ , and additivity.

Although these are derived from the results for toluene<sup>98,99</sup> they are almost identical with the predictions made by Reddy<sup>39</sup> who did not examine the tetra- or pentamethylbenzenes, and did not comment on deviations shown in the trimethylbenzenes. The values shown in brackets are mean positions.

(b) This correlation was achieved by allowing a reduction of 0.05ppm in the effect of a "buttressed" ortho methyl group, and a reduction of 0.07ppm in the effect of a "flanked" meta methyl group.

### (3) Interpretation of the Correlations

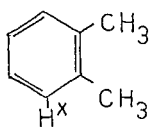
The concepts of buttressing and flanking are not unambiguous. For "flanked ortho" (e.g.

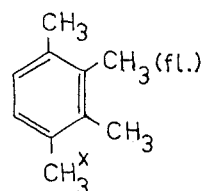
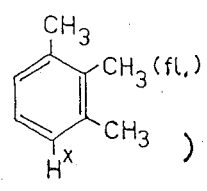


the effect could as well be described as an interference



with the transmission of the meta effect as by a modification of the ortho effect. The fact that the reduction is 7.5 standard deviations greater than the total free meta effect makes the former description unattractive.

For "buttressed ortho" (e.g. ) the same alternatives are possible. In this case the meta effect is large enough to account for the observed reduction, but analogy with the "flanked ortho" favours a similar interpretation.

The two "flanked metas" (e.g.  ) could be interpreted as the result of double buttressing of the ortho or para groups, or as a modification of the meta effect. No distinction appears possible from this work.

Although the special correlating effects used to account for the methyl and ring proton shifts are similar, only the "flanked methyl" modifications can be directly compared. The reduction in the effect due to flanking a meta methyl group is four times larger on a ring proton than on a methyl proton. This value is similar to the ratio of three observed for the transmission of many substituent effects.

Clearly, a methyl group ortho to an observing methyl group cannot be "unbuttressed", and a methyl group ortho to an observing proton cannot be "flanked". Comparison

of these two modifications is therefore impossible.

#### (4) Physical Model for Chemical Shifts

The physical model used to account for chemical shifts employs the following effects.<sup>34,35</sup>

- (a) Diamagnetic screening from the circulation of electrons on the same atom as the nucleus in question. This effect is regarded as being strongly correlated with electronic charge densities.
- (b) Paramagnetic corrections from the same source as (a).
- (c) The combined effect of the diamagnetic and paramagnetic currents on other atoms.
- (d) Effects due to ring-currents.

Diamagnetic susceptibilities for polymethylbenzenes have been derived from crystal measurements and are expected to be valid for liquid and gaseous states. Using a semi-empirical method the following values have been obtained by Dorfman.<sup>100</sup>

TABLE 24

Diamagnetic Susceptibilities of the Polymethylbenzenes

	<u><math>-\chi_d \cdot 10^6</math></u>	<u>Additivity</u>	<u><math>\chi_p \cdot 10^6</math></u>
Benzene	65.00	-	10.15
Toluene	77.00	-	10.90
o-Xylene	89.00	89.00	11.22
m-Xylene	89.50	89.00	12.97
p-Xylene	90.00	89.00	13.09
Mesitylene	102.00	101.00	10.00
Durene	114.00	113.00	12.20
Hexamethylbenzene	144.00	137.00	21.50

It can be seen that additivity for the diamagnetic term ( $\chi_d$ ) is obeyed very well except for hexamethylbenzene. This latter result was interpreted as due to an increase in ring current, and the great increase in the paramagnetic term ( $\chi_p$ ) was also attributed to this cause. In the absence of results for other members of the series the hexamethylbenzene result is hard to explain. Curiously, ortho-xylene gives the lowest value of the three xylenes.

As has already been observed, increasing ring current does not explain the N.M.R. results for hemimellitene and isodurene, where only some methyl groups deviate from additivity.

Shielding effects of the anisotropy of aromatic systems due to ring currents appear to be well understood, and can

be calculated with confidence.<sup>101</sup> The situation with respect to the anisotropies of C-C and C-H bonds, of a methyl group for instance, is less clear and several interpretations have been made.<sup>102,103</sup> As in the present case the problem is often to separate charge densities (a), from anisotropies (c).

### CONCLUSION

The rate-constants for detritiation at all the free ring positions of the polymethylbenzenes have been determined. The results are approximately correlated by the Additivity Principle, but reactivities of the more highly substituted members of the series are consistently over-estimated.

The importance of various second order effects within the framework of the Additivity Principle have been investigated, and it seems that steric interaction with the reaction site is not substantial. The largest deviations from additivity appear to occur when para substituents are present, but the general failure of the principle with increasing substitution obscures any particular interactions.

To account for the falling off of the rate enhancement as reactivity increased it was assumed that the contribution of a substituent was proportional to the free energy of activation. For ortho and para substituents, satisfactory agreement with this prediction was found. For meta methyl groups a substantially greater rate of fall off was observed, which was interpreted as a consequence of the lack of resonance interaction with the reaction site. The effect of the meta methyl group must then be strongly dependent on the charges developed at the adjacent ortho and para positions, and so will be markedly reduced

when substituents in these positions are electron donating.

Assignment of a small part of the activation energy to describe interaction with the two meta positions allowed estimates of the sensitivity of the meta methyl groups to be made, and the results confirmed the expected order of effects: para > adjacent ortho > non-adjacent ortho >> other meta ~ 0.

Agreement still lies outside experimental error (although least-squares refinement of the parameters has not been attempted), and it seems likely that other factors are also operating.

The N.M.R. results appear to show no steric influence on the effect of changing from n-hexane to carbon tetrachloride as solvent. Both ring and methyl proton chemical shifts can be correlated by an additivity relationship only if proximity effects are allowed for. Thus the substantial effect of a neighbouring methyl group is reduced when a further methyl group is placed alongside the first.

Considerable work on rotational barriers presently in progress has shown that two adjacent methyl groups have restricted rotational freedom, and three adjacent methyl groups exhibit complex rotational motions which have not yet been interpreted.<sup>104</sup> As rotational barriers are commonly of about 2 kcal/mole, it is apparent that any involvement

of these complications in activation energies of the detritiation reactions could well cause substantial deviations from additivity.

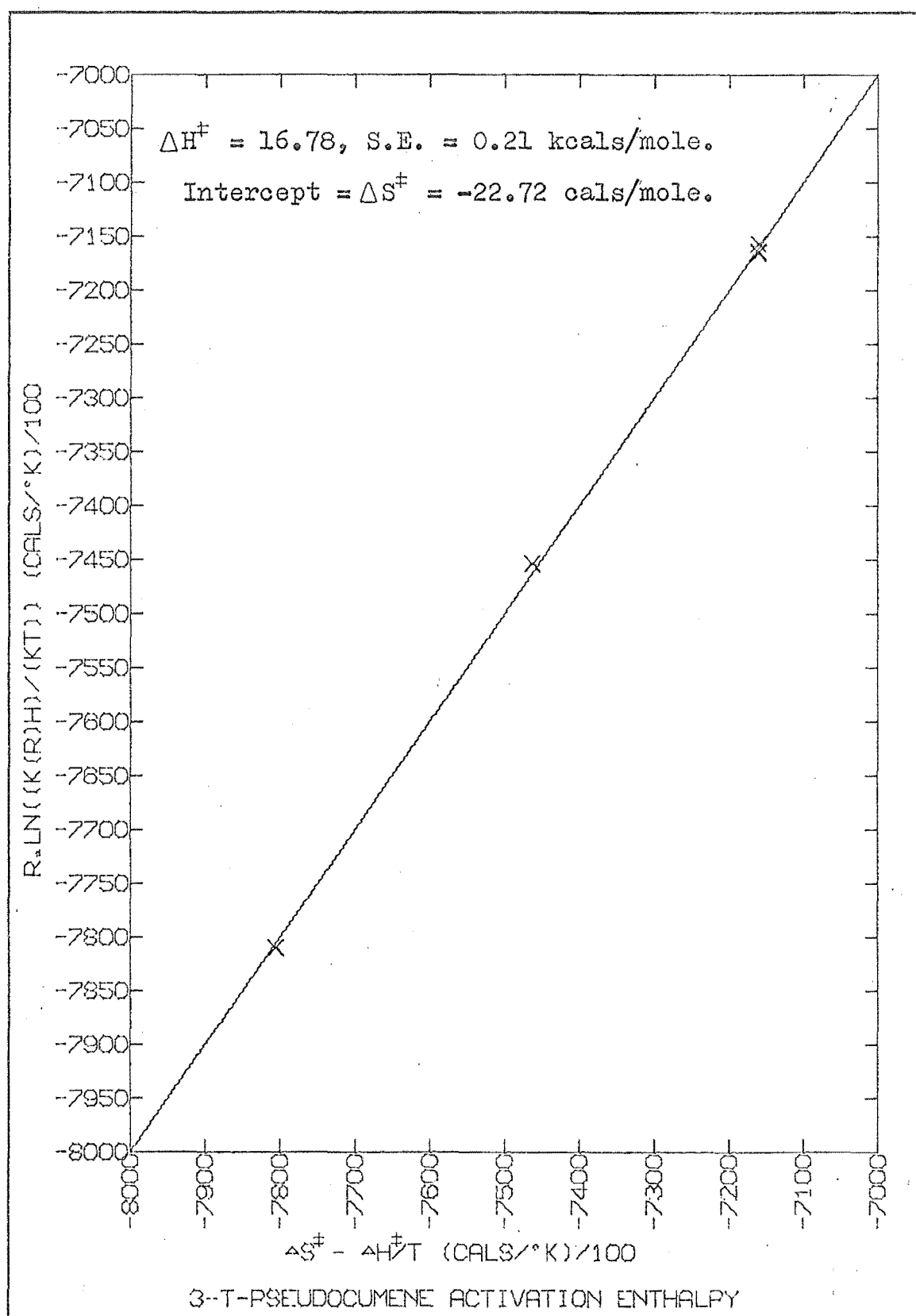
Similarly, rotational motions could well be important in the short-range shielding effects of the ortho methyl groups shown by the N.M.R. measurements.

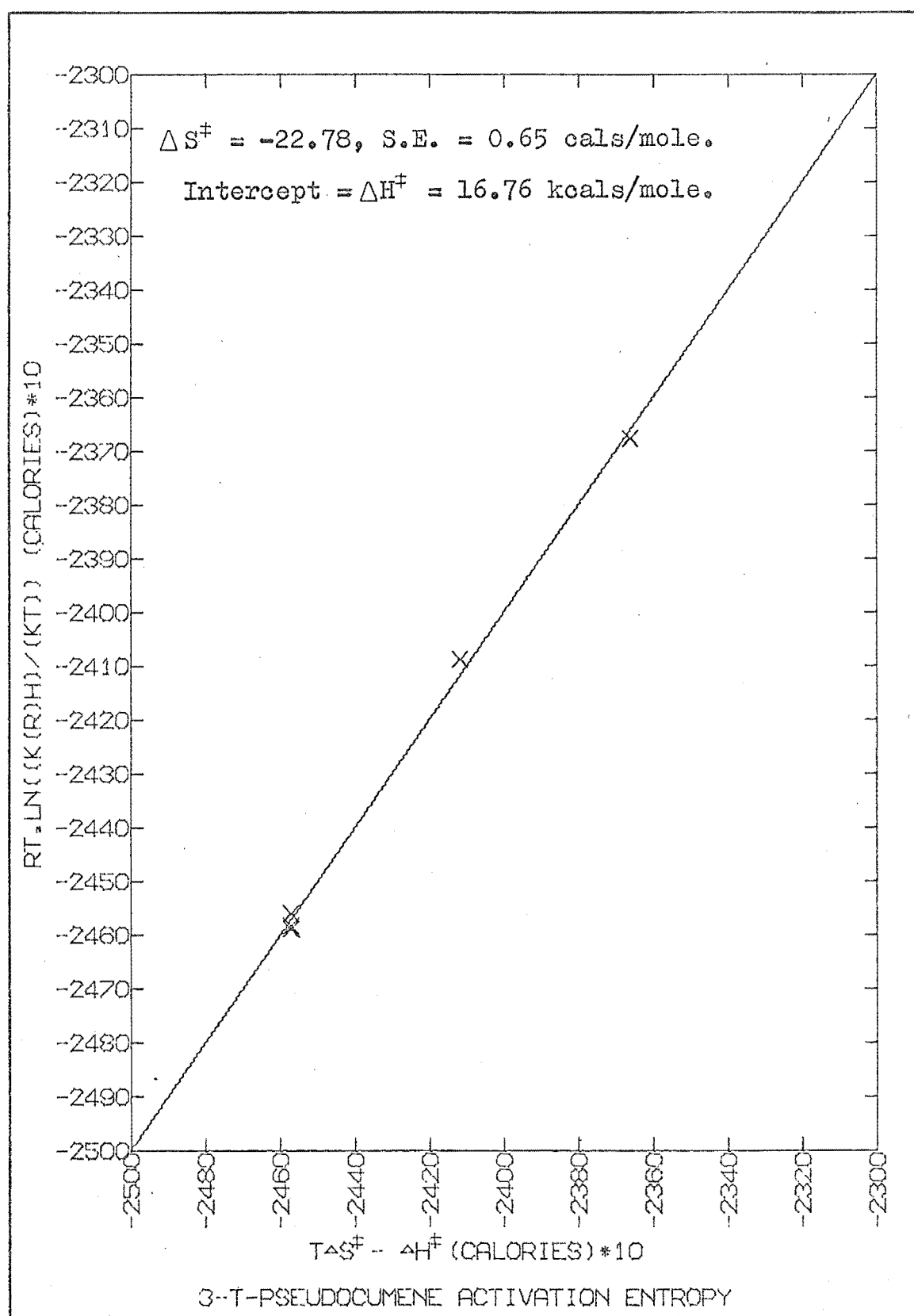
Examination of the Additivity Principle for a substituent of cylindrical symmetry could resolve these possibilities.

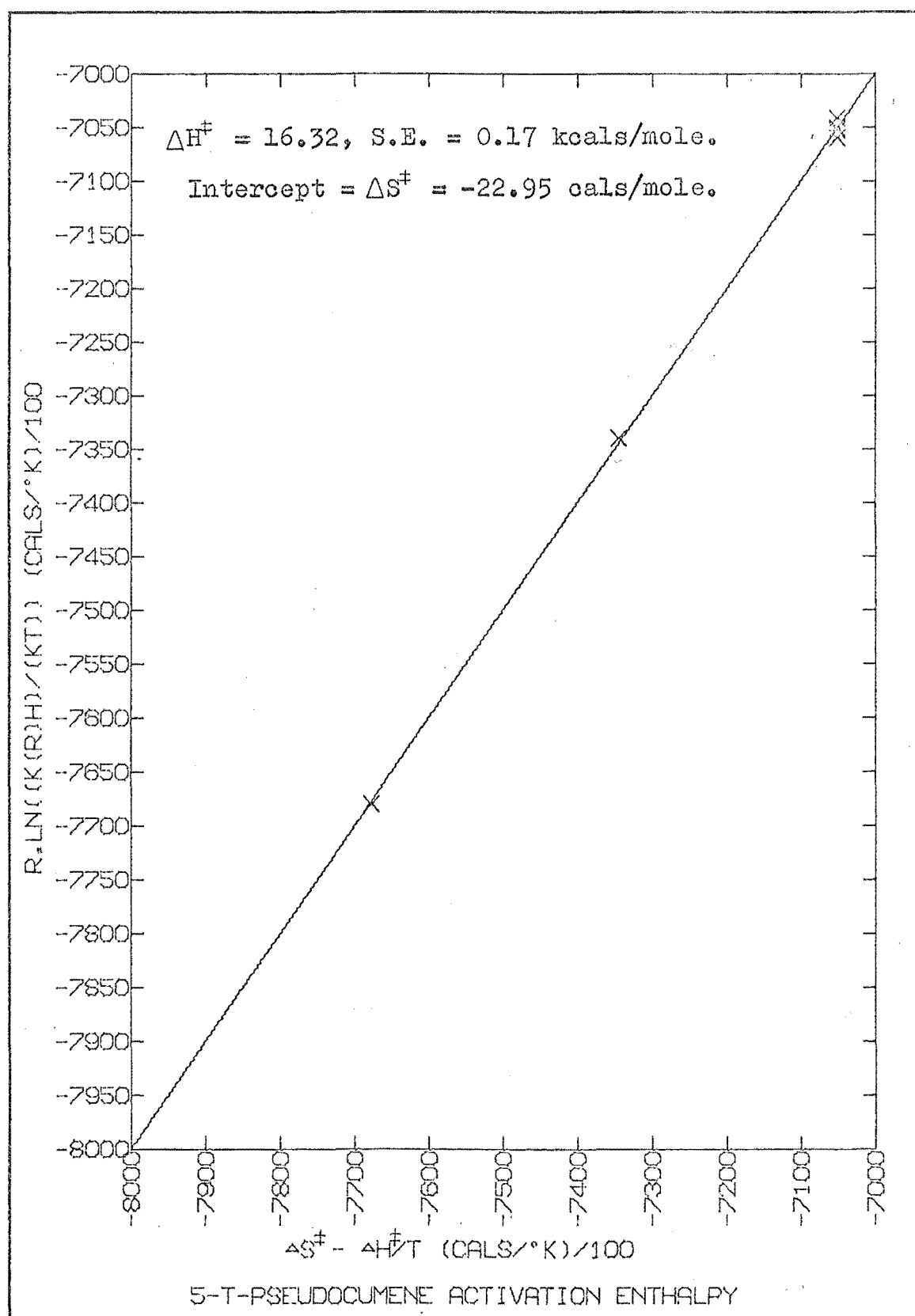
APPENDIX(i) Temperature Dependence of the Rate of Detritiation

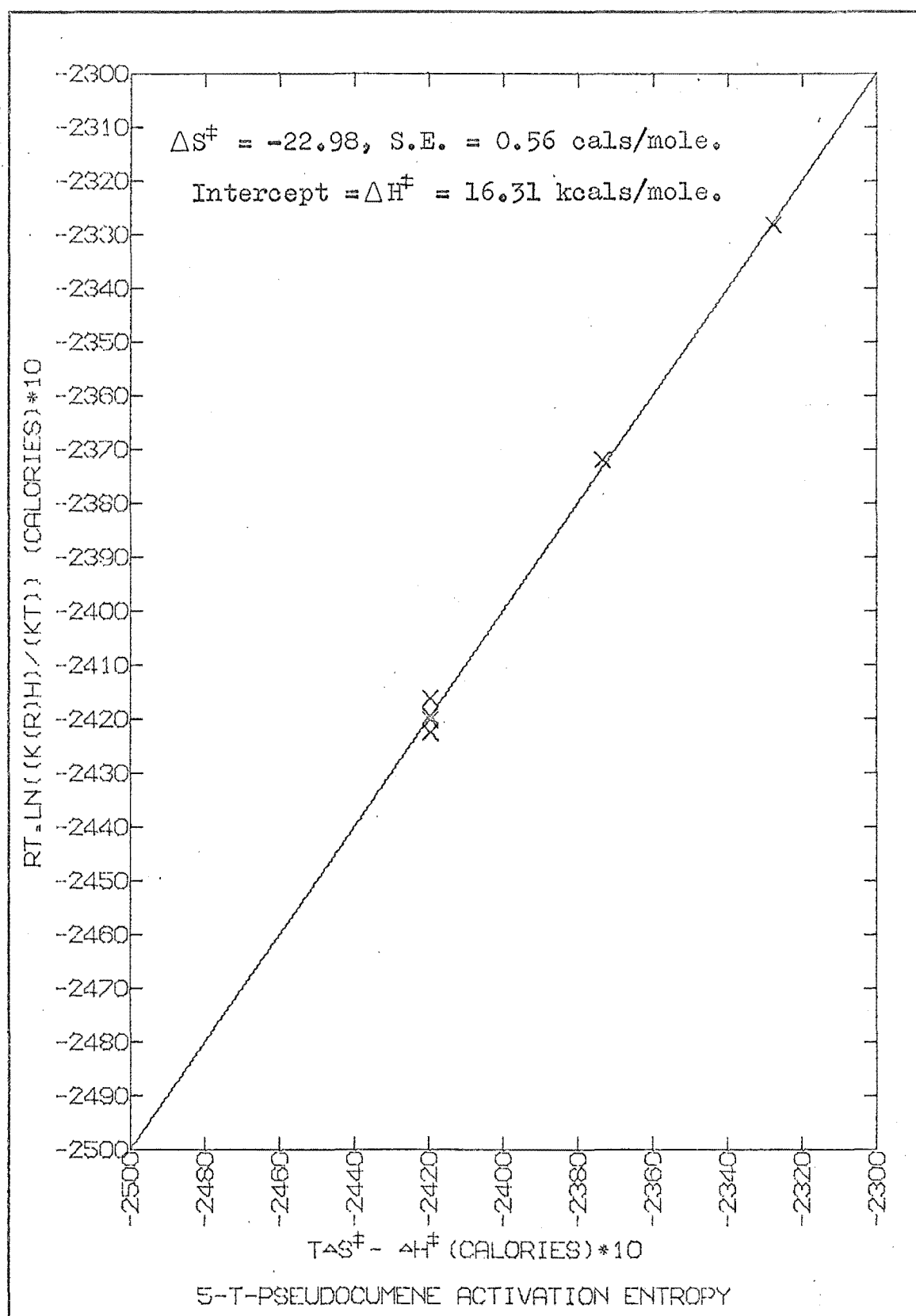
Graphs showing least-squares correlations between functions of the rate-constants of detritiation and functions of the absolute temperature at which the reactions were conducted are shown in the following pages. For each of the four tritiated compounds examined two plots are shown one of which has slope  $\Delta H^\ddagger$  and the other  $\Delta S^\ddagger$  according to the absolute rate theory equation (page 82). The results of the analyses are shown in Table 4.

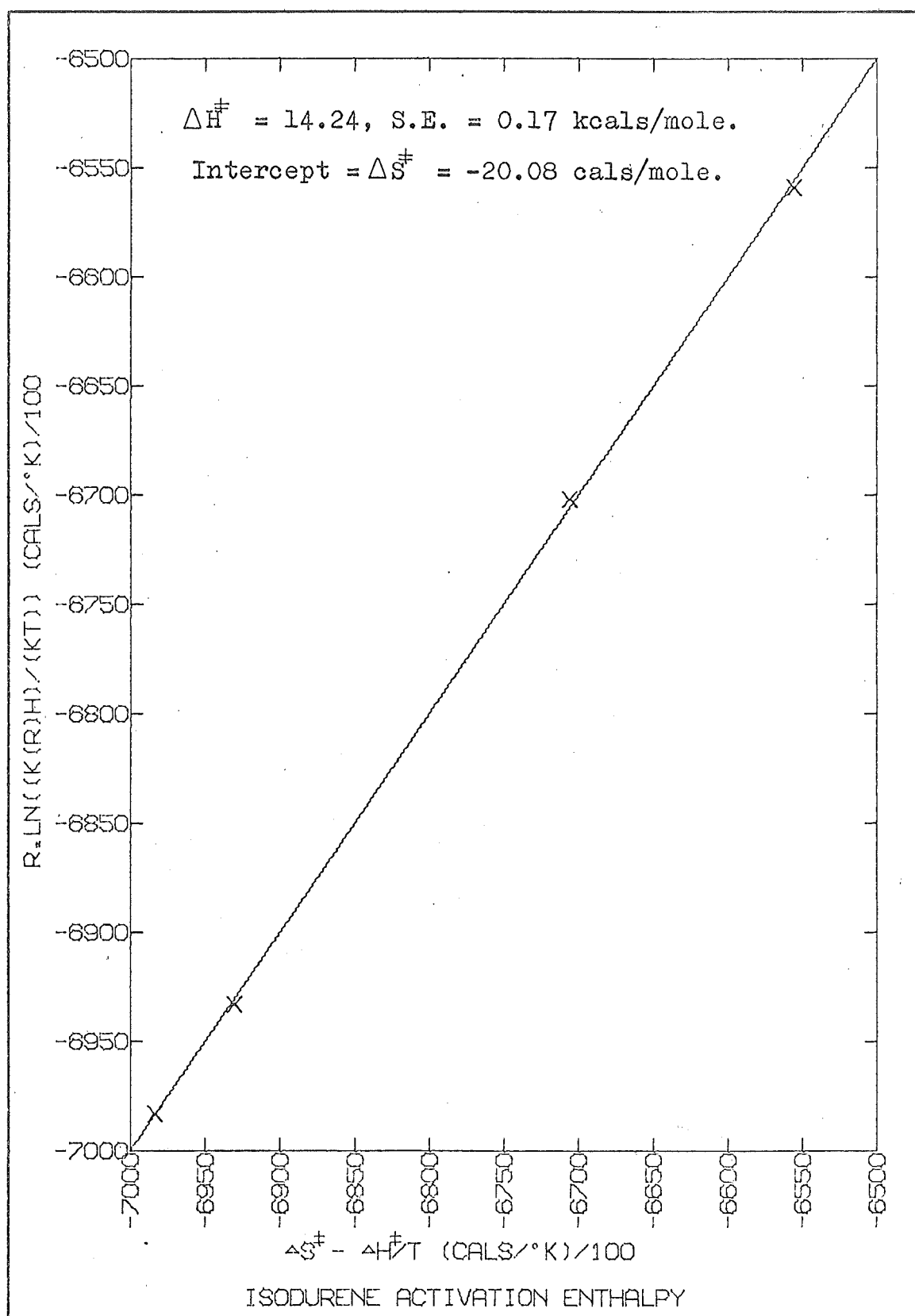


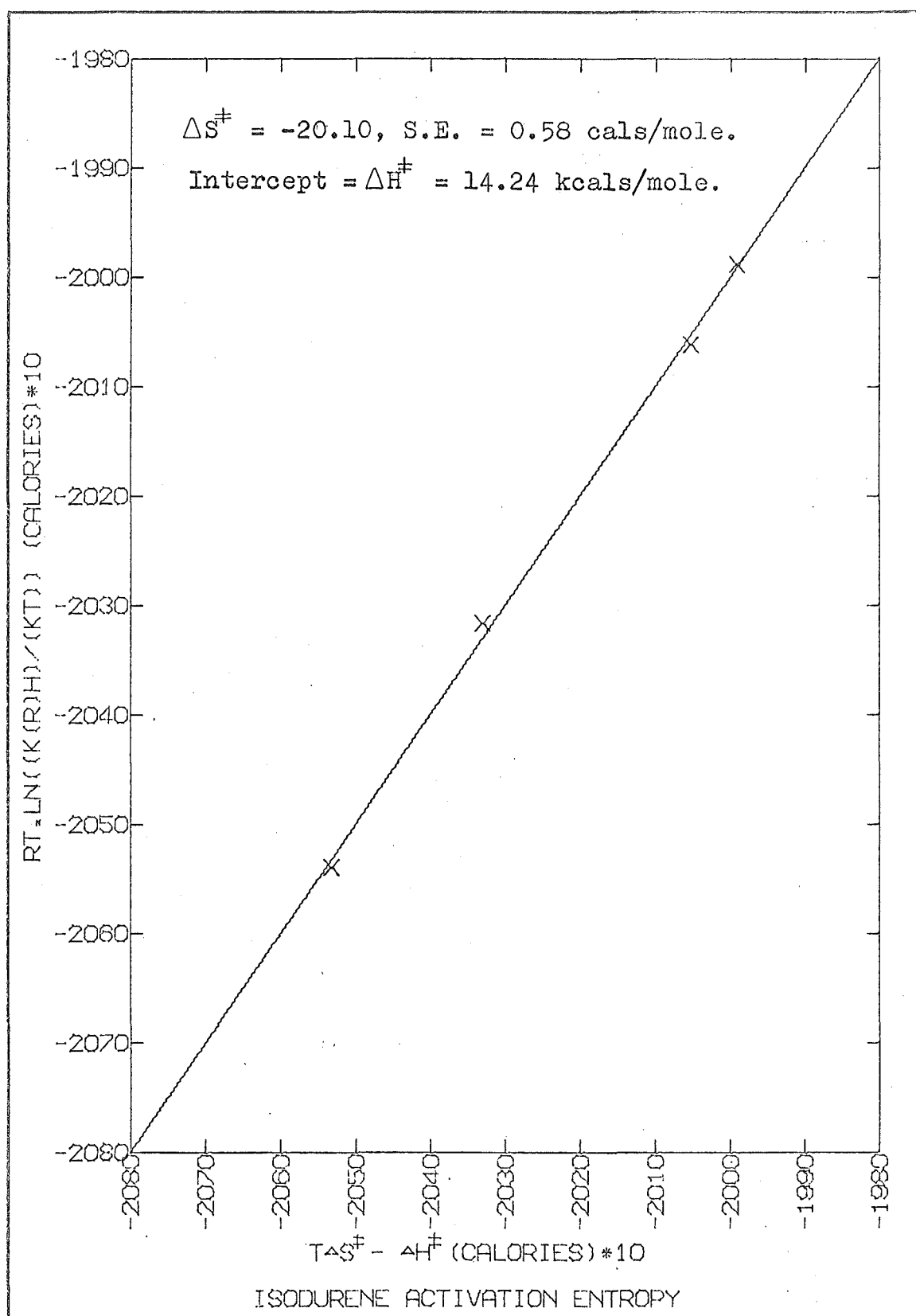


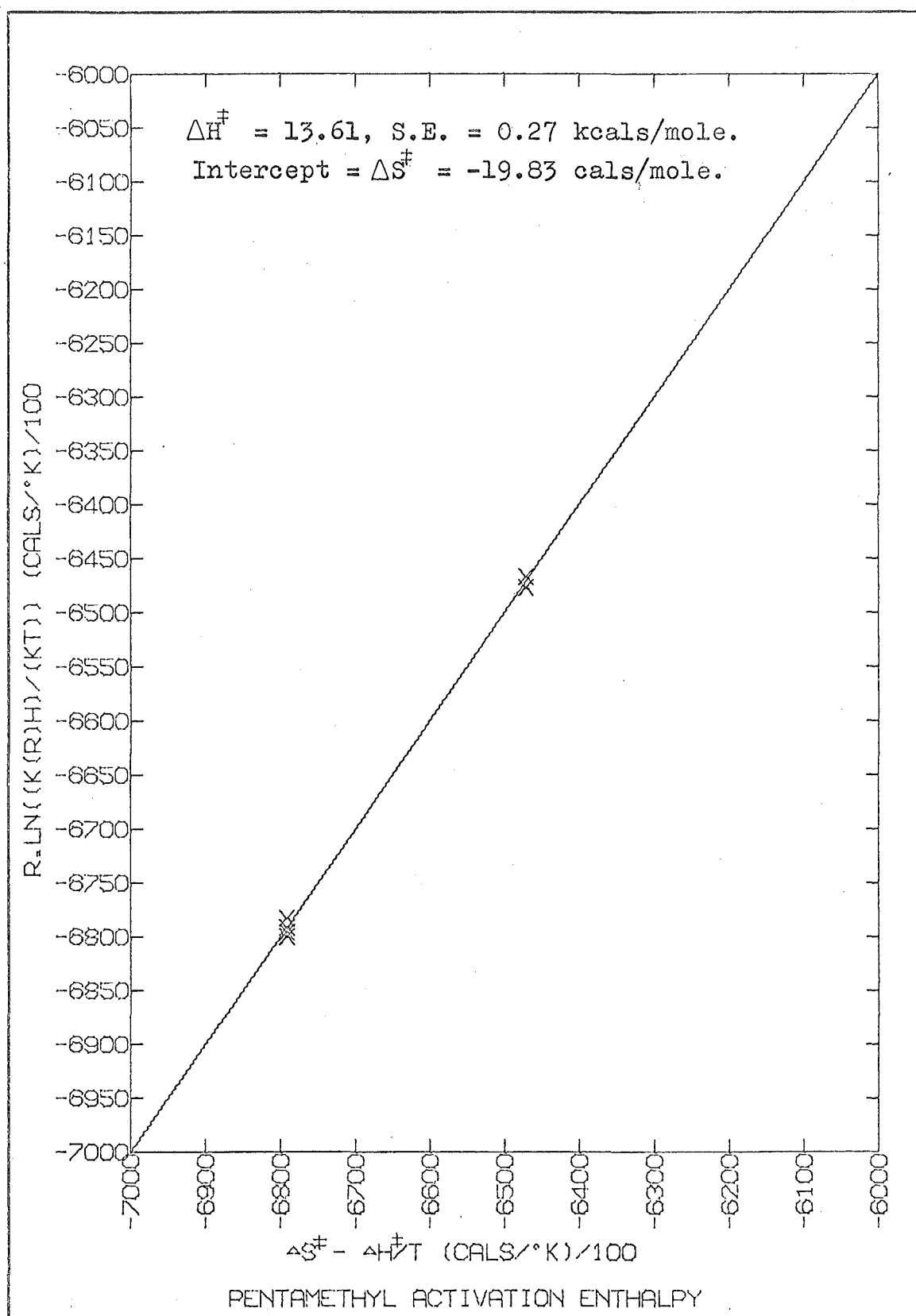


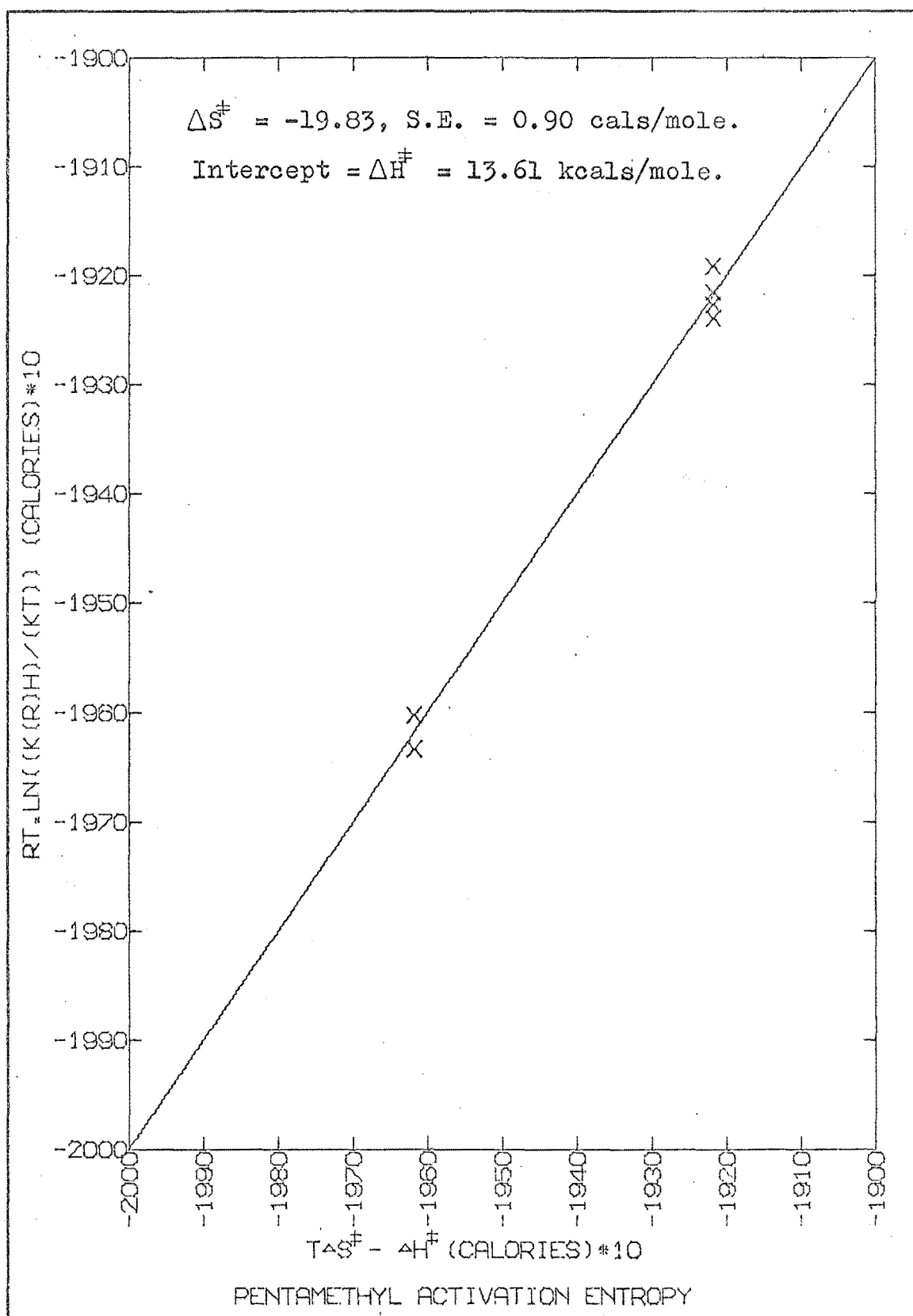














(ii) Trivial Names of the Polymethylbenzenes

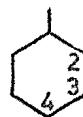
The trivial names of the polymethylbenzenes are shown on the following page together with the numbering convention used in this thesis.

TRIVIAL NAMES OF THE POLYMETHYLBENZENES

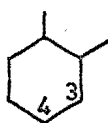
Methyl groups are represented by lines and aromatic  $\pi$ -bonds not shown. Non-equivalent ring hydrogen atoms are numbered.



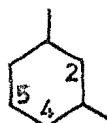
benzene



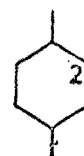
toluene



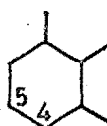
o-xylene



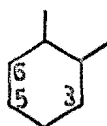
m-xylene



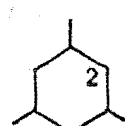
p-xylene



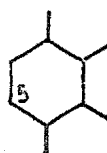
hemimellitene



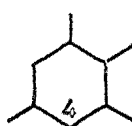
pseudocumene



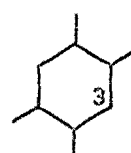
mesitylene



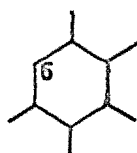
prehnitene



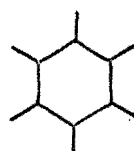
isodurene



durene



pentamethyl-  
benzene



hexamethyl-  
benzene

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N.B. Two series of reviews frequently referred to have been abbreviated.

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